Article

False-Positive Results of Radionuclide Imaging in Lactating Breasts: *a pharmacovigilance perspective*

Vojislav Kišić[1*] and Jennifer Parish[2]

[1]University of Belgrade School of Medicine, Dr. Subotića 8, 11000 Belgrade, Serbia.
[2]IQVIA, Leskoškova cesta 2, 1000 Ljubljana, Slovenia.

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ABSTRACT

Background: Misleading diagnostic results, including false-positives, potentially impact both the safety and efficacy profiles of radiopharmaceuticals used for diagnostic purposes. It is unclear, however, if false-positives occurring with radiopharmaceuticals in lactating breasts are regularly reported as adverse events.
Methods: Scientific medical literature (PubMed and Google Scholar) and the EudraVigilance database of suspected adverse drug reaction reports were searched for case reports of false-positives with radiopharmaceuticals appearing in lactating breasts. Medical Dictionary for Regulatory Activities (MedDRA) was reviewed for terms that could be used to capture reports of false-positives occurring in breast nuclear imaging accurately.
Results: Literature searches showed that 40 case reports of false-positives have been observed with radiopharmaceuticals in lactating breasts but that these do not appear to be consistently reported to EudraVigilance as adverse events. MedDRA did not contain terms suitable for capturing false-positives in breasts with radiopharmaceuticals, but newly proposed terms were all approved.
Conclusion: Increased reporting of false-positives as adverse events could help further clarify the safety specification of radiopharmaceuticals.

KEYWORDS:

Radiotracers, lactation, pharmacovigilance, adverse events, false-positives

INTRODUCTION

Nuclear medicine provides a form of imaging that contributes to evidence-based patient care across a variety of medical disciplines. This includes extensive applications in oncology, particularly with regard to the staging and prognostic management of patients with malignant neoplasms. Nuclear cardiology encompasses a functional assessment of the heart, including myocardial perfusion and ventricular function, for a variety of cardiac pathologies. Nuclear neurology investigates various metabolic patterns of the central nervous system. The use of radionuclide imaging has been found in endocrinology, infectious diseases, and gastroenterology (1).

Radiopharmaceuticals are pharmaceutical products containing radionuclides used for the diagnosis, staging, and therapeutic management of pathological processes throughout the body (2). Diagnostic radiopharmaceuticals are designed to facilitate imaging of specific processes in target tissues. The mechanism of action for these drugs involves their collection in body sites based on the function of the target tissue. As such, it is sometimes considered that radiopharmaceuticals elicit no physiological responses or adverse reactions from patients (3).

Both physiological and pathological changes in metabolism can lead to increased uptake of radiopharmaceuticals. While the increased uptake in target tissues is inherent to the mechanism of action for these drugs and is essential for their efficacy, "true-positive" imaging results due to disease processes need to be clearly distinguished from "false-positives" due to the normal variations in the metabolic activity of healthy tissues. Common physiological causes of increased uptake of some radiophar-

* Correspondence to: V Kišić, email: vojislavkisic@gmail.com, or J. Parish, email: Jennifer.Parish@IQVIA.com

maceuticals include the high metabolic activity of specific tissues such as the brain, heart, and kidneys. Transient increases in the metabolism of other tissues, such as the skeletal muscles after exercise, can also show increased uptake of some radiopharmaceuticals.

Two key attributes distinguish an actual "false-positive," or *FP*, from a case of benign increased uptake. Firstly, an FP mimics another illness that has a similar imaging presentation. Secondly, an FP affects the decision-making process for patient management (4). Therefore, any additional diagnostic or treatment process, including additional history-taking or physical exam, triggered by the appearance of increased uptake of a radiopharmaceutical should cause that imaging result to be considered an FP.

Pharmacovigilance, the monitoring of drug safety in order to ensure the maintenance of a positive benefit-risk balance, is a moral and ethical obligation of all pharmaceutical companies (5). Special populations are groups within the general population that have unique pharmacovigilance benefit-risk considerations. This can include patients with renal impairment, the elderly, children, and pregnant or lactating women. Despite having specific needs that can impact drug utilization decisions, children and pregnant women are generally excluded from clinical trials due to ethical concerns. All women of childbearing potential (WOCBP) are often also excluded in order to reduce the possibility of inadvertent fetal exposure due to unintended pregnancy during a clinical trial (4, 6). Although it is recommended to investigate the excretion of pharmaceutical products in human milk when feasible, many lactating females are also WOCBP, and may also be pediatric patients (7). This complex overlap in special populations is illustrated in **Figure 1**. As such, post-marketing safety monitoring is the most important source of information for understanding the breastfeeding-related safety profile of many medicinal products.

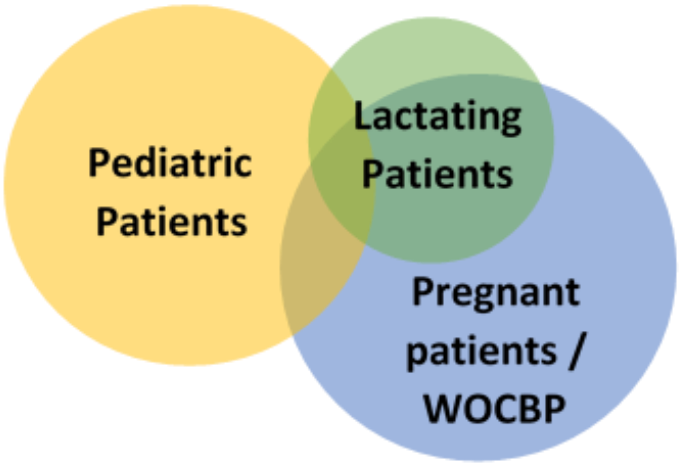

Figure 1. Lactating patients overlap with other special patient populations that are often excluded from clinical studies

In addition to their frequent exclusion from clinical trials, lactating women are also likely to be excluded from other organized data collection systems, such as breast cancer screening programs (due to their relatively younger age). As a result, information that may help reduce FP imaging results in lactating breasts may be underrepresented in clinical data, which could have some clinical implications. Approximately 6 percent of breast cancer cases are diagnosed in women under the age of 40 years who did not undergo the standard screening for breast cancer and who also tend to be diagnosed at later stages with more aggressive forms of cancer (8); abnormal breast imaging results in younger women can prompt more aggressive diagnostic and treatment plans. Given that younger patients may also be lactating women, adequate knowledge to distinguish true positives from FPs is essential for these patients in order to prevent unnecessary, invasive diagnostic procedures. This overlap between young breast cancer patients and other special populations is highlighted in **Figure 2**.

Positron Emission Tomography (PET) is usually not recommended for breast cancer screening but is instead reserved for whole-body imaging during advanced disease staging and evaluation. This is due to a relatively high rate of FPs, resulting in both low sensitivity and specificity of the method (9). This pitfall of PET may significantly increase the risk of incorrect diagnostic and therapeutic judgment; therefore, FPs should comprise an important part of the safety specification of radiopharmaceuticals used during PET imaging. Breast findings may also be noted incidentally on PET scan when performing evaluations of malignancies where lesions in the breasts were highly unlikely to be found. It has been reported that the rate of malignant neoplasms in breasts found unexpectedly on PET scan is between 27.3% and 83.3% (10). The high variability of this estimate may be explained by the relatively high degree of FPs in breasts on PET imaging.

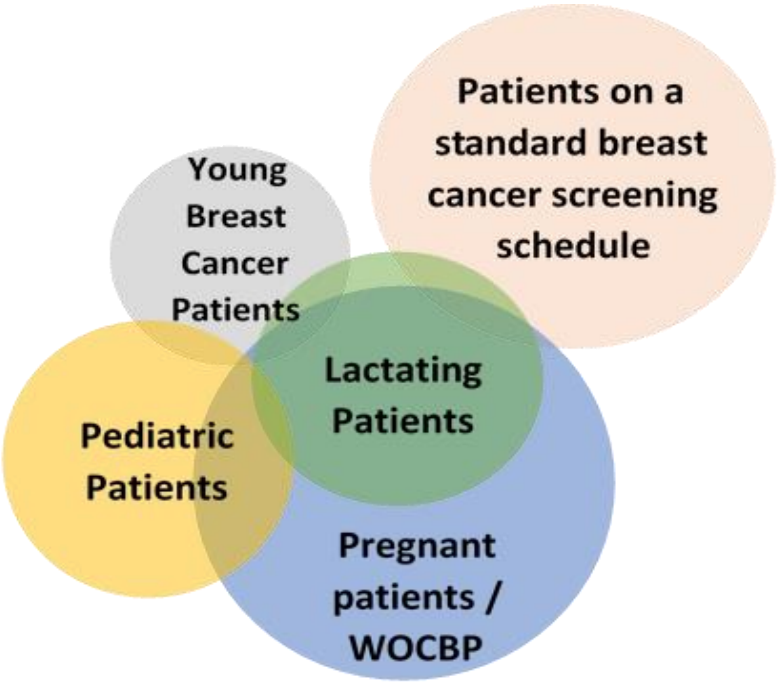

Figure 2. Young breast cancer patients are likely included in other special patient populations, including lactating women

Radiopharmaceuticals such as 18F-Fludeoxyglucose (18F-FDG), Technetium (99mTc) Pertechnetate, 99mTc Sestamibi, and Gallium (67Ga) can detect diseased breast tissue. 18F-FDG uptake in breasts occurs with certain types of breast neoplasms, including invasive ductal carcinoma and invasive lobular carcinoma, and in a variety of benign conditions such as mastitis, fat necrosis, fibroadenoma and atypical ductal hyperplasia (11). 99mTc Pertechnetate uptake in breasts has been observed in conditions, including mastitis and breast cancer (12). 99mTc Sestamibi is currently used for radionuclide imaging of breasts (13). 67Ga is a radiotracer used for the localization of tumors and inflammatory processes, including those affecting breasts (14). The increased metabolic activity that occurs during lactation (15) would suggest that lactating patients would be likely to experience FPs during radiopharmaceutical imaging. Therefore, it is reasonable to suspect that the above-mentioned radiopharmaceuticals would most likely be associated with FPs in lactating breasts.

As in many regions that follow the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use ("ICH") guidelines, the European guidelines on product packaging and information for radiopharmaceuticals include information relevant to FPs. The European Medicines Agency (EMA) "Guideline on core SmPC and the package leaflet for fludeoxyglucose" indicates that Section 4.4 of the Summary of Product Characteristics (SmPC) should include specific text regarding the interpretation of imaging results in consideration of the potential for false-positives (16). The guideline, however, does not include lactating breasts in the list of tissues prone to providing false-positive results. It is also unclear as to whether FPs with radiotracers are regularly considered to be, or reported as, adverse events (AEs).

The objective of this paper is to examine the extent to which false positives during breast nuclear imaging reported as adverse events in EudraVigilance for radiopharmaceuticals is consistent with the number of reports available in the literature. These results were used to propose updated MedDRA terms, pharmacovigilance tools that may contribute to a positive clinical impact for lactating women undergoing radiopharmaceutical imaging involving the breasts.

METHODS

A search of scientific medical literature was performed to identify potential cases of FPs obtained with radionuclide imaging in lactating women. On December 12 2018, PubMed and Google Scholar were searched for articles published up to and including the date of search. PubMed was searched using the string ("radiopharmaceuticals" [Pharmacological Action] OR "radiopharmaceuticals" [MeSH Terms] OR "radiopharmaceuticals"[All Fields]) AND uptake [All Fields] AND ("lactation"[MeSH Terms] OR "lactation"[All Fields] OR "breast feeding" [MeSH Terms] OR ("breast"[All Fields] AND "feeding"[All Fields]) OR "breast feeding"[All Fields]). Google Scholar was searched with the following three search strings *allintitle: fdg breastfeeding OR breastfeed OR lactating OR lactation OR breast "false positive"; allintitle: pertechnetate uptake breastfeeding OR breastfeed OR lactating OR lactation OR breast;* and *allintitle: gallium uptake breastfeeding OR breastfeed OR lactating OR lactation OR breast.* Each literature article was assessed for the presence of data-elements needed to construct a valid Individual Case Safety

Report (ICSR) as specified in the EU individual case safety report implementation guide publ-ished by the EMA (17). The country listed in the primary authors' address was considered to be the country of occurrence of the FP.

A search of a publicly available database of AE reports was performed to identify reports of false-positives that potentially occurred in association with lactation. On December 13, 2018, the EudraVigilance European database of suspected adverse drug reaction reports (ADRreports) (18) was searched for all reports of FPs with 18F-FDG, 99mTc Pertechnetate, 99mTc Sestamibi, and 67Ga received cumulatively as of November 2018. To account for potential overlap between cases of increased uptake and FPs, cases containing any event terms referring to misleading investigation results were reviewed. This included all Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms (PTs) and synonyms containing 'scan abnormal' (e.g., PT *Radioisotope scan abnormal*) as well as PT *False-positive investigation result*. To help identify any cases potentially occurring with lactating breasts, we also searched cases for the PT *Maternal exposure during breast feeding*.

A search of MedDRA and the MedDRA change request portal "WebCR" was performed to identify any term or combination of terms that currently exist or had been previously proposed for addition to MedDRA, which could be used to capture FPs occurring during radiopharmaceutical imaging of breasts. In cases where no single "combination term" is available to adequately capture the relevant medical information in an event, the recommendation from MedDRA is to "split" the event across two or more PTs. If a split term remains insufficient to code the event, the recommendation is to submit a change request suggesting a new, more descriptive MedDRA term (19). Based on the terms identified during the literature, ADR-reports and MedDRA searches, a MedDRA change request was submitted with newly proposed terms.

RESULTS

The search of PubMed identified 23 relevant articles and Google Scholar retrieved an additional 17 articles. Of these articles, nine contained case reports, including a total of 11 patients, and described an evident FP for radiotracers in lactating breasts. Each of the cases included the four data elements, as described in the EMA Guideline on Good Pharmacovigilance Practices (GVP) that could potentially qualify for reporting as an ICSR (20). Eight of the articles originated from outside of the European Economic Area (EEA) and all case reports from these articles could have been assessable as having included non-serious events, consistent with their exclusion from the ADRreports database. The key information regarding each article is listed in Table 1.

Table 1. Journal articles containing events of false-positive results in lactating breasts in 11 patients.

Product	Year	Patient(s) (Sex, Age)	Author	Country of occurrence*	Title
Fludeoxyglucose (18F)	2018	F, 36y	Ceyrat, et al. (24)	France	*Galactocele, Pitfall for the Evaluation by 18F-FDG PET/CT*
	2013	F, 38y	Ko, et al. (21)	Korea	*Diffuse intense 18F-FDG uptake at PET in unilateral breast related to breastfeeding practice*
	2012	F, 32y	Abhyankar, et al. (25)	India	*FDG uptake in unilateral breast related to breastfeeding practice in a patient of pulmonary hydatid cyst*
	2010	F, 32y	Hendler and Stemmer (22)	Israel	*Uncommon reason for high fluorodeoxyglucose positron emission tomography uptake*
	2009	F, UNK F, UNK F, UNK	Li, et al. (26)	China	*Pitfalls in positron emission tomography/computed tomography imaging: causes and their classifications*
	2002	F, 28y	Shor, et al. (27)	USA	*Asymmetric FDG uptake in a lactating breast*
	1998	F, 38y	Yasuda, et al. (28)	Japan	*Lactating breast exhibiting high F-18 FDG uptake*
Technetium (99mTc) Pertechnetate	2013	F, 5d	Jain, et al. (29)	India	*"Witch's milk" and 99mTc-pertechnetate uptake in neonatal breast tissue: an uncommon but not unexpected finding*
Technetium (99mTc) Sestamibi	1996	F, 30y	Sutter and Stadalnik (23)	USA	*Noncardiac uptake of technetium-99m sestamibi: an updated gamut*

Abbreviations: D = Day; F = Female; UNK = Unknown; USA=United States of America; Y = Year; *, Based on the country of author.

The search of the ADRreports database identified a total of 20 reports pertaining to the concerned radiopharmaceuticals. Of these, three were reported to have occurred in females up to age of 64 years and none of them contained information indicative of use during lactation: none included the PT *Maternal exposure during breast feeding*. Of these three ICSRs, one was from a literature article from the United States describing a false-positive radionuclide imaging result unrelated to the breasts or lactation that was assessed as serious (30). No reports were found pertaining to Technetium (99mTc) Sestamibi or Gallium (67Ga). The radionuclides and associated MedDRA PTs identified in the ADRreports database are shown in **Table 2**. The cumulative search results of the EudraVigilance database are shown in Table 3.

Table 2. Reports from the ADRReports database including *PT False-positive investigation result* for radiopharmaceuticals used in women aged up to 64 years

Product	Year	Patient(s) (Sex, Age)	Reporter	Reported MedDRA Terms (PT)	Seriousness
Fludeoxyglucose (18F)	2015	F, 32y	Grove, et al. (21)	False-positive investigation result	S (Other)
Technetium (99mTc) Pertechnetate	2015	F, 56y	HCP	Bone scan abnormal	S (Other)
	2018	F, 33y	HCP	Radioisotope scans abnormal No adverse event	NS

Abbreviations: F = Female; HCP = Health care professional; NS = Non-serious; PT = Preferred term; other = other medically important condition; S = Serious; Y = Year

Table 3. EudraVigilance search results (cumulative, up to November 2018)

Product	Number of abnormal scan results	Abnormal scan results in women aged up to 64	Containing MedDRA PT *Maternal exposure during breast feeding*	MedDRA PT
Fludeoxyglucose (18F)	2	1	0	False Positive Investigation Result
Technetium (99mTc) Pertechnetate	10	1	0	Radioisotope scan abnormal
	5	1	0	Bone scan abnormal
	1	0	0	Lymph node scan abnormal
	1	0	0	Renal scan abnormal
	1	0	0	Ventilation-perfusion scan abnormal
Technetium (99mTc) Sestamibi	0	0	0	/
Gallium (67Ga)	0	0	0	/
Total AEs	**20**	**3**	**0**	/

Abbreviations: AE= Adverse event; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred term

As of December 2018, MedDRA did not contain a term for FPs in breasts with radiopharmaceuticals. The MedDRA terms available at that time, which are most appropriate for use in reporting an FP during the use of radiotracers were PT *Radioisotope scan abnormal* and PT *False positive investigation result*. However, no terms were available to indicate that these results occurred in the breasts. The search of WebCR indicated that no terms have previously been proposed that could more completely capture such events. Therefore, the nine terms shown in **Table 4** were submitted as change requests to the MedDRA Maintenance and Support Services Organization (MSSO) via WebCR on December 20, 2018. In January 2019, all nine terms were accepted by MSSO. These change requests also prompted the inclusion of one additional term, PT *Breast scan abnormal*. All ten terms were included in MedDRA version 22.0, which was released in March 2019.

DISCUSSION

Literature search results indicate that uptake of 18F-FDG, 99mTc Pertechnetate, 99mTc Sestamibi, and 67Ga has been observed in lactating breasts in both asymmetric and symmetric patterns. Asymmetric uptake patterns due to unilateral breastfeeding practice appear to be an important challenge for image interpretation as they can easily produce FPs. Unilateral breast accumulation of the concerned radiopharmaceutical during breastfeeding, especially 18F-FDG, may appear suggestive of advanced breast cancer, lymphoma, or an inflammatory condition. Usually, mass or inflammation is ruled out using non-invasive diagnostic techniques such as concomitant computerized tomography (PET/CT), additional history taking, mammography, breast ultrasound or even delay in radionuclide imaging until the patient ceases breastfeeding (12,21-23,31,32). Rarely, invasive diagnostic modalities such as biopsy are used to evaluate misleading diagnostic results (24). Our literature search results indicate that FPs occurring due to lactation appears to be a well-recognized risk among nuclear medicine imaging experts.

Despite their inclusion in literature articles, FPs occurring during lactation do not appear to be routinely reported as AEs to EudraVigilance: no reports pertaining to the occurrence of an FP in lactating women were found in the ADRreports database. Given that 10 of the 11 cases of FPs retrieved during the literature review were from non-EEA countries, it is not surprising that these did not appear as ICSRs in the ADRreports database: non-serious AEs occurring outside of the EEA are not reportable to the EMA (18). Nonetheless, our literature search results indicate that FPs occurring in the breasts during lactation are not uncommon. As such, the lack of at least one ICSR related to these FPs in the ADRreports database is an unexpected finding. No previous literature articles summarizing similar discrepancies between identification and reporting of false-positive results were identified.

Table 4. Currently available MedDRA terms and newly accepted MedDRA terms potentially relevant for events of false-positive results in lactating breasts

Concept	Similar Current MedDRA Terms	Comment	Newly Accepted and Added Terms and Hierarchy
PET scan of the breast	PT Radioisotope scan abnormal PT Positron emission tomogram abnormal PT Nuclear magnetic resonance imaging breast abnormal	*Specific to PET but not to the breast*	In HLT Reproductive organ and breast imaging procedures PT Positron emission tomogram breast
	PT Computerised tomogram breast abnormal	*Specific to the breast but not to PET*	PT Positron emission tomogram breast abnormal
	PT Mammogram abnormal PT Ultrasound breast abnormal		In HLT Imaging procedures NEC PT Breast scan abnormal
	PT Breast scan	*Although specific to the breast, this unqualified term is inappropriate for reporting of adverse events.*	LLT Radioisotope scan breast LLT Radioisotope scan breast abnormal
False-positive	PT Iodine uptake increased	*Applicable only to imaging with iodine and, although related, abnormal or increased uptake is not sufficient to create a false-positive*	In HLT Imaging procedures NEC PT Radioisotope uptake increased
	PT Iodine uptake abnormal		In HLT Reproductive organ and breast imaging procedures
	PT False positive investigation result	*Does not specify investigation or tissue*	PT False positive radioisotope investigation breast result
Lactation	HLT Lactation disorders	*All currently available PTs referencing lactation are included in this HLT. As such, none are appropriate for coding lactation as part of anamnestic data or medical history*	In HLT Normal pregnancy, labor and delivery PT Lactation normal In HLT Reproductive organ and breast histopathology procedures LLT Breast feeding unilateral LLT Breast feeding bilateral

Abbreviation: PET=Positron Emission Tomography; PT=Preferred term; HLT=High level terms; LLT=Lowest level term; NEC=Not elsewhere classified

The low prevalence of FPs reported as AEs for radiotracers used in lactating women may be attributable to a perception that radiopharmaceuticals are not associated with AEs (3) or that FPs are not AEs. The evident discrepancy between the prevalence of these reports in the literature and ADRReports database may indicate a lack of consensus in classifying FPs as either Special Situations that do not require reporting or actual AEs comprising one of the four data elements of an ICSR. It may be argued that isolated FPs without any additional untoward consequences (e.g. not requiring further changes in diagnostic/therapeutic management) could be considered Special Situations rather than AEs *per se* (33). The crux of this argument would rest on determining which additional interventions triggered by FPs would be considered "noxious or unfavorable outcomes." While the minimally-invasive or non-invasive nature of additional history-taking or physical exams may lead healthcare providers to consider the FP is not a true AE; patients and/or regulators may take a different perspective. Of note, cases found in the ADRreports database included isolated events of PT *False positive*, suggesting that the EMA considers these FPs to have been valid AEs in ICSRs containing all four required data elements whatever the justification for their classification as either special situations or true AEs, clarification on the handling of FP reports could contribute to the safety specification of these products, particularly with regard to lactating women, a Special Population (34).

MedDRA terminology is designed to facilitate AE reporting. A consistent approach to the selection of MedDRA terms contributes to the understanding and interpretation of pharmacovigilance data among academics, pharmaceutical companies and regulators (19). The MedDRA WebCR portal is designed to facilitate submission of change requests but also serves as a source of information on other previously submitted change requests and their reasons for acceptance or rejection (35). A review of the MedDRA WebCR change request submission history indicated that there had not been any terms previously proposed that relate to FPs for radiopharmaceuticals. Even when used as split terms, the MedDRA terms available in v21.1 could not allow for an event of false-positive radioisotope test results in the breast to be adequately identified during data retrieval. Submission of a MedDRA change request proposing the addition of MedDRA PTs specific to these events may facilitate the reporting of FPs in lactating breasts with radiotracers. After the addition of these terms to MedDRA in v22.0, future reviews of AE databases may indicate if this MedDRA change request helped facilitate the increased reporting of such adverse events.

Limitations of this research included the use of only the publicly available information from the ADRreports data-

base. As such, the narrative portions of the case reports, which may have included references to false-positives that had not been captured as event terms, were unavailable for review. Additionally, this data was collected from spontaneous reporting systems, which is routinely limited by the risk of underreporting. To overcome these limitations in futures studies, the inclusion of other databases of AEs, (e.g., the FDA Adverse Event Reporting System (FAERS) or VigiBase, the WHO database of Adverse Events) or the use of solicited AE reporting sources (e.g., clinical trials), may provide further insight on the actual status of FPs in nuclear medicine imaging of lactating breasts reported as AEs.

CONCLUSION

There is an evident discrepancy between the ADRreports database and scientific medical literature with regards to reporting FPs in lactating breasts with radiopharmaceuticals. Literature searches indicated that cases of FPs have been observed with radiotracers in lactating breasts but that these do not appear to be reported as AEs to EudraVigilance. Future potential avenues of research include assessing to what extent the newly accepted MedDRA terms have facilitated the reporting of FPs during imaging of lactating breasts with radiopharmaceuticals.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest regarding the publication of this paper.

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