Deanship of Graduate Studies

Al-Quds University

Analysis of Tumor Markers Effect after Radiation Exposure among Palestinian Radiation Workers

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Dedication

I want to dedicate my work to my family.

To all my friends, colleague, professor.

Thank you all.

Areej Dahdol

Declaration

I certify that this thesis submitted for the degree of Master is the result of my own research, except where otherwise acknowledged, and that this study (or any part of the same) has not been submitted for a higher degree to any other university or Institution.

Areej Najeeb Ali Dahdol

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Date: 07 June 2020

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Abstract

Objective: The aim of this work was to investigate the effect of low radiation doses on tumor markers tests. And to follow up the policy that carrying out the tests for Radiation Workers. Also, demonstrate the effect of independent variables such the cumulative dose, Hospital location, and type of work on tumor markers.

Method: the researcher reviews a retrospectively collected database of tumor marker tests in four governmental hospitals +between 2013- 2019, to follow~~ing~~ the patterns of tumor marker over the years. The cumulative doses records were taken from energy department in ministry of health. Additionally to distribute a questionnaire to correlate independent variables with tumor markers records and also to demonstrate the policy following of carrying out these tests among RWs. 78 radiation workers participated.

Results: after several years of following tumor markers, all tumor markers tend to increase in a normal range, especially the CEA; approximately 57% of radiation workers have an increase in CEA. The smoking workers have a statistically significant change in CEA; also the study not shown any relationship between the radiation doses and tumor markers. While a measure of the knowledge level of policy show 73% of worker answered that no one is responsible for following test~~s~~ results. Further, 91% of workers admit no action was taken in the event of an abnormal result found.

Conclusion: Until now all tumor markers results was in a normal range, even if they tend to a little increase from year to year, but that still prove nothing without repeat this study and comparing this group of worker with another different type of workers, to understand if this increase that have noticed here in this study come from radiation or not. Otherwise highlight the role of policy officer who’s responsible for monitoring the carrying out these tests and follow up what happen on radiation workers tests results.

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List of Abbreviations

Abbreviation	Representation
TMs	Tumor markers
RWs	Radiation workers
CEA	Carcinoembyronic antigen
CA125	Carbohydrate Antigen 125
CA19-9	Cancer antigen

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Chapter One

Introduction

1.1 Introduction

Cancer in radiation workers has increased over the years **(Choi et al. 2013).** This facts lead to build a recommendation in cancer detection and protection of RWs. According to that, tumor marker (TM) tests are effective in indicating the presence of a tumor. The term usually refers to a molecule that can be detected in plasma or other body fluids **(Nagpal et al. 2016).** The researcher studied the relationship between low radiation doses and their effects on tumor markers among RWs. And believes this study contribute to understand the effect of chronic low radiation doses that occupational worker exposed to.

1.2 Problems Statement

The biggest reason for following a TM test is to highlight the effect of low radiation doses on tumor markers, which helps to understand how radiation effects on radiation workers. Besides, early cancer diagnosis will manage treatments especially among RWs, who need more protection. Alternatively, in order to measure how much the policy of carrying out TMs test followed by our hospitals.

1.3 Objective

1.3.1 General Objective:

The main purpose was to study the low radiation doses effects on TMs, especially cancer, which may occur as a stochastic effect from occupational radiation work.

1.3.2 Specific Objectives:

- Explore the knowledge level of following TMs policy among RWs.
- Assess TM tests over several years of working in radiation department.
- Correlate TMs with independent variables such as (the cumulative dose, Hospital, type of work).

1.4 Research Hypothesis

Hypothesis 1: there is no correlation between the cumulative dose and TMs.

Hypothesis 2: there is no correlation between the Hospitals and TMs.

Hypothesis 3: there is no correlation between the type of work and TMs.

Chapter Two

Literature Review

This chapter reviews some literature, published studies and an analysis of the low radiation dose effects on medical radiation workers. Specifically the cancer which conceder a stochastic effects that come from radiation exposure. Also address the tumor markers as a tool used for detection of cancer.

2.1 Introduction

Occupational radiation workers are more likely to receive low doses of radiation over a long period of time. The basic of low doses radiation effect is non-lethal mutations, with the biggest concern being the induction of cancer. The concern comes from that some radiation risks are correlated to dose by a linear, no-threshold model. Briefly LINEAR means, there is a proportional relationship between the dose and the risk. And NO-THRESHOLD means, any dose, no matter how small, may cause some risk **(Calabrese and O'Connor 2014).** Actually, the low radiation doses effect is still under discussion, ICRP (2005) reveals that; estimation of radiation-related risk at low doses is based on extrapolation of risk observations at moderate to high doses. Also, the risk of mortality and morbidity from cancers is proportional to radiation dose down to about 100 mSv, the Epidemiological data are useful about radiation-related risks at acute doses, and to some extent, low (~10 mSv) dose ranges, but not in the very low (~1 mSv) and extremely low (~0.1 mSv) ranges. The most important single problem in radiation risk protection is how to extrapolate the risk of lower radiation dose levels that are of greater concern in our life **(Valentin J. 2005).** In this study the doses were (less than 10 mSv) also it's so important to understand the effect of these range of doses that RWs chronically exposed to.

Several recent studies have shown evidence on cancer among occupational worker. One study using human peripheral blood lymphocytes to asses the DNA damage and antioxidant status show the chronic low radiation dose exposure is an unavoidable hazard leading to oxidative stress, increased genomic instability, and a rise in cancer among RWs **(Siama et al 2019).** In addition, the incidence of thyroid cancer rates is higher among

Korean RWs than the general population **(Lee et al. 2018; Lee et al.2019).** Also study on health risks shows an increase in all of skin lesions, orthopedic illness, cataract, hypertension, and hypercholesterolemia in cardiac catheterization workers **(Andreassiet al. 2016).** Another study focused on reliable cancer mortality risks from a low-dose in a nuclear industry, show evidence of stochastic effects and statistical significance for lung cancers. **(Qu et al. 2018).** Based on that, this leads you to conclude this population needs more intensive protective measures and development tools for early detection cancer that being proven, safe, and acceptable test (**Schiffman et al. 2015).** Tumor biomarker considered as one of most important tools, referred to secreted molecule in blood from tumor in case of cancer presence. Although radiation detection field show that, an assessment of absorbed dose by using a protein with gene expression, will consider a good biomarker of radiation. But the insufficient sensitivity and specificity of tumor marker test make a positive result does not necessary indicate the presence of a cancer. That means additional procedures (such as biopsy or x-rays...etc) is needed in conjunction with these tests. **(Sahoo 2018; Kayaba 2003; Rana et al.2010)**

Some tumor markers are used for screening such as Carcinoembryonic antigen (CEA) is a glycoprotein, the elevated levels found in colorectal, breast, lung, or pancreatic cancer and, in smokers **(Bhatt et al.2010)** But have special sensitivity among markers for colorectal cancer **(Gao et al. 2018)** Another is Cancer Antigen 19-9 is most commonly used for pancreatic cancer **(Scarà 2015).** While the regular CA19-9 measurements show improve in early detection of biliary tract cancer. Also, Carbohydrate Antigen 125 is tumor marker for ovarian cancer. However, study shown a combining betweenCA125 with human epididymis protein 4 (HE4) improve the sensitivity and specificity to ovarian cancer (**Wannhoff 2019)**

However, several studies have reported that multiple markers are more useful in detection of some cancer. Some study reported that the combining of CA 19-9, CEA and others markers will increase sensitivity and specificity in Gastric cancer, additionally other studies have shown that combining them also contributes to diagnoses and predicting of pancreatic cancer. Also combing of CA19-9 and CA125 has shown to encouraging sensitivity for pancreatic cancer. **(Kotzev et al. 2018; Li et al. 2013; Meng et al. 2017; O'Brien et al. 2015)**

2.2 Previous Studies

The effect of some tumor markers also the effect of high background radiation on them has been studied. A Study in 2019 in the field of Biomarkers present that, the serum 8-OHdG which is a biomarker oxidative stress, levels was found to be significantly higher in interventional radiology workers**. (Gao et al. 2019)** also study in Ramsar (Iran) shown that there is significant alteration in Cyfra21, CEA, and Tag72 levels due chronic exposure to high background radiation. **(Taeb et al. 2014)** Although a study monitoring cytogenetic using micronucleus assay among RWs shows that the chromosomal damage leading to micro-nucleated lymphocytes is more frequent between exposed workers **(Sari-Minodier et al . 2007).** The researcher believes the study of tumor markers might help highlight on low radiation effects, especially cancer, among the workers who’s exposed to chronic low doses.

Chapter Three

The Method

This chapter provides the framework of the study, including the statistics that were done for TM tests over the years, in addition to an evaluation of other factors related to TMs.

3.1 Study Design

A retrospective study was performed by collected data about the patterns of TM tests over Years the questionnaire was structured to determine the factors affecting test results, also assessing the policy of carrying out these tests were studied.

3.2 Study Population

The study populations in this study are the RWs working in the four governmental Hospitals in Palestine.

3.3 Study Sample

The sample was 78 RWs, who responded to questionnaires

3.4 Inclusion Criteria

Work with diagnostic modalities that utilize ionizing radiation.

3.5 Exclusion Criteria

1. Worker with disease was avoided to accuracy the results, (some disease elevated TMs value like hepatic disorders, diabetic…..etc. because of that any kind of disease was excluded).

2. Work with diagnostic modalities that do not utilize ionizing radiation (like MRI, U/S).

3.6 Data Collection

After institutional review board approval, the researcher reviewed retrospectively collected database of tumor marker tests in four Governmental Hospitals between 2013- 2019, to following the patterns of TM tests over the years. The test records are distributed as follows, 42 record of CEA, 45record of CA 19-9, 35 record of CA125 that done over the years of the study. Reach to independent variables such as Hospital location, smoking status and the type of work by structured questionnaire, also the knowledge level assessment of following the policy done by the questionnaire. While the dose recorded was taken from database of Energy Department in Palestinian Ministry of Health.

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3.7 Statistical Analysis

The researcher analysed the collected data by using SPSS program version 22. Student's t-test and one-way ANOVA was used for testing the equality of the means in the groups. P value <0.05 was considered as significant. Descriptive statistical analysis was using to determine the tumor marker behavior along several years and to assessment the following of policy among RWs.

3.8 Ethical Consideration

Approvals were taken by formal letters that were sent from Al-Quds University to the *Ministry of Health (MoH*), in which the study purpose was explained. Official permission was given to visit the Hospitals to distribute the questionnaires and to facilitate data collection procedures. The participants' Consent form was a one-page information sheet attached to the questionnaire. Participants take full explanations about the research, including the purpose and nature of the study before submitting the questionnaire. Also, the participants were assured confidentiality of the information and their privacy by communicating using code instead of using their real names. The researcher gave total freedom to accept or reject participation in this research (Appendix 1 & 2)

Chapter Four

Results and Discussion

This chapter introduces results, including means, percentages, and frequencies of responses for each item. Achieving the purpose of the study requires many questions to be answered and discussed.

4.1 Socio-Demographic Characteristics of the Respondents

In the beginning, this study reached to ninety-three RWs, but only seventy-eight (78) questionnaires filled, giving a response rate of *83.8 %*. The characteristics of RWs are shown in **figure (4.1).** Briefly, Hospital A occupied 34%. While 66% of participants were distributed equally by Hospitals B, C, and D. *60%* of RWs were less than 35 years of age, 51% had less than ten years of working experience. Approximately 88% of participants have bachelor degrees. Also 91% of study participants were a male. And 59% of them non-smokers. These ratios are normal because the distribution of universities leads to a rise in education. The male dominance is understandable because females have an apprehension from working in a hazardous workplace, especially during her pregnancy. All this leads to the fact that most sample was from men, so the effect of gender was not studied. Also, the CA- 125 it considers as marker for ovarian cancer but combined with others marker show elevated in pancreatic cancer **(O'Brien et al. 2015).** When look back at our goals, the researcher finds that 63% worked with CT scans and X-rays, in fact, the X-ray faculty require more staff than interventional procedures.

The **figure (4.1)** also illustrates one of the most important questions of this research which is, how much do you undergo TMs examination?? As seen more than half of RWs have no systemic of performing a test. Only 49% of RWs are carrying out TMs every year as they should do, this question was done to compare it to another question that will mention below.

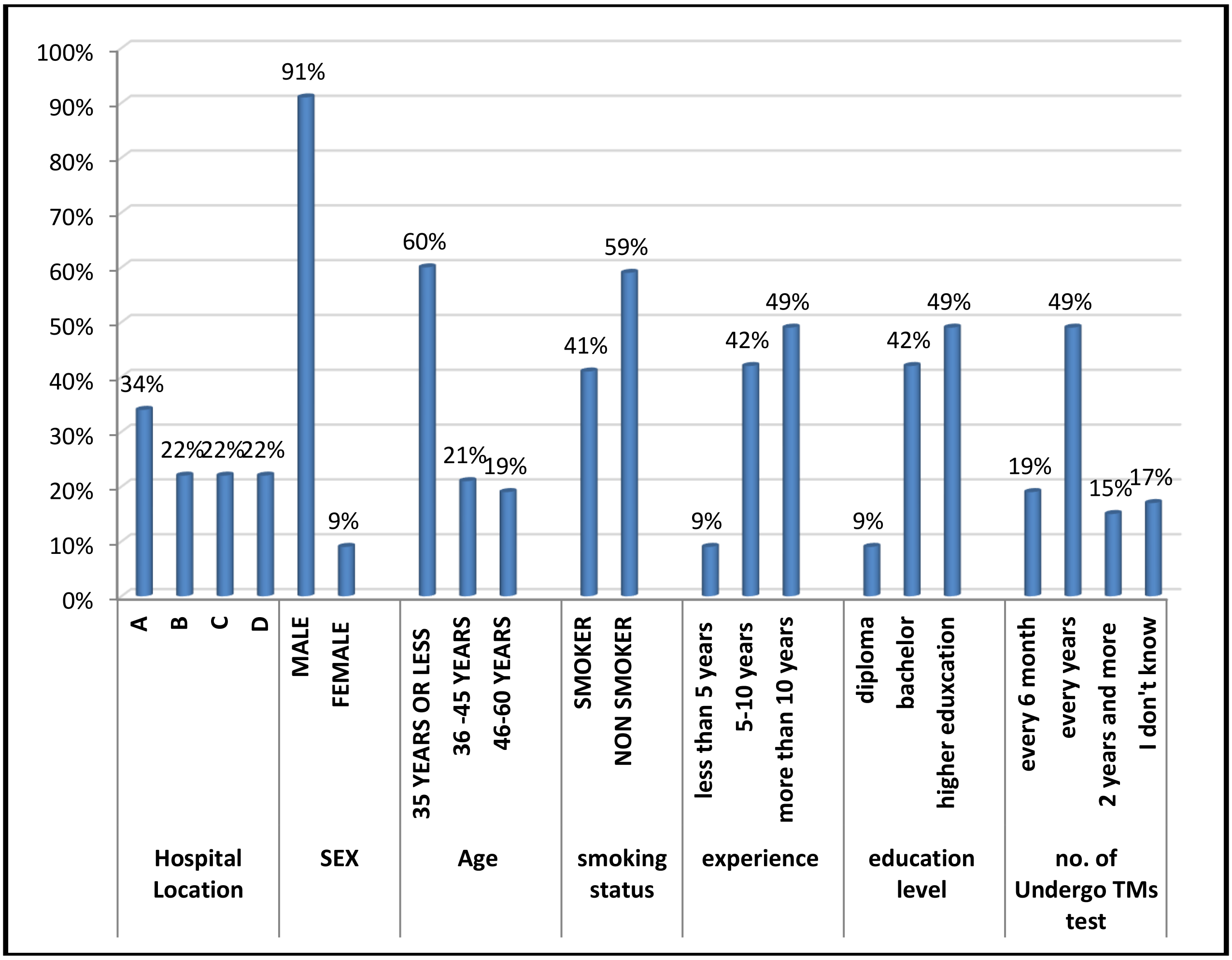

Figure (4.1) Distribution of the characteristics data by percentages for each independent variable

4.2 Measurement of Tumor Markers Policy among Radiation Workers

At First, short questions of the compliance with TM policy performance. With a total of 78 respondents. As shown in **table (4.1)** use of an electronic system in governmental Hospitals make 67% of RWs said their tests saved in records, also 73% of RWs answered that, TMs results are not followed by anyone, which brings researcher to the point, there is no responsible person or even a policy officer to follow what is happening or even to see if tests are being performed. In addition, 53% of RWs claim that they do TM tests regularly, and this, however, goes against the records which show irregularly performing of test. 74% of RWs known about their results, but that leads researcher to conclude; it’s not necessarily informed by a responsible person, and this is because RWs can follow with laboratory.

Moreover, 63% of RWs think that radiation affects TM results, this corresponds to the elevated level of education among RWs (88% had B.Sc.) as mentioned above which mean there is some awareness on the low doses effect, but unfortunately to the best of our knowledge there is lack of research especially in Palestine on radiation biology field and how low radiation doses effect our body. Finally, *91%* of RWs admit that if they acquire an abnormal result, no policy is there to act or to investigate what is happening, which is the same point, mentioned above, there is no policy-officer responsible for monitoring test results in the radiation department.

Table (4.1) Percentages of knowledge level of tumor markers policy among radiation workers

Items	Yes		No		I don’t know	
	Number	%	Number	%	Number	%
Are you informed about your test result no matter what it is?	58	74%	13	17 %	7	9%
Is this test saved in the technical records?	52	67%	6	8%	20	26%
Are the test results followed by responsible people?	21	27%	28	36 %	29	37%
Are you carrying out this test regularly?	41	53%	25	32 %	12	15%
Do you think radiation exposure may affect the results of this test?	49	63%	11	14 %	18	23%
Is there any action taken if there is a variation in the result?	7	9%	28	36 %	43	55%

4.3 Assessment of Tumor Markers Test through Years

One of the most important questions asked in this study; what happens to TM test over several years of work in the radiation department? According to **table (4.2)** which represents the percentages of how TM tests behave over the years (from 2013 -2019). The TM test pattern is expressed by scale levels (decrease, increase, and stable). The unstable state, however, is ignored because of unclear behaviour. When return to **table (4.2)** the researcher found that ***57%*** have an increased in CEA TMs, but within the normal range of (0-5 ng /ml) **see figure (4.2 A**). Just one RW has abnormal results in the CEA. This reminds us on the alteration occurrence in CEA levels in a high radiation background. **(Taeb et al. 2014).** These finding may highlight on CEA as a most sensitive TM to radiation, due to the highest percentage of increase among TMs, being more stable and having the lowest percentage of decrease over the years. The elevated CEA may appear in case of lung cancer (**Bhatt et al.2010),** while the lung considers as the organ sensitive to radiation with risk factor at 2.0 $*10^{-3}$ Sv[1] **(Till & Grogan 2008),** also as shown in **table (4.3)** the smoking have significantly different (p=0.01) in CEA TM. This significant differences was in favor of the RWs who are smokers, thus, coinciding with other studies that proved that smoking affect CEA markers **(Bhatt et al. 2010; Nan et al. 2017)** and that may be little interpreted this increase.

However, CA-19-9 and CA125 have an increase about 46% and 54%, respectively. Also find a tendency for a decrease of 31% and 37%, respectively, with a very low percentage of stability in CA-19-9 and CA125 as TMs. but all the increase and decrease over the years for all TMs within the normal range as see in **figure (4.2 A, B and C)**. Overall, the increased pattern was the most behaviour TMs have followed. Although, as mentioned in more than one study, the combination of TMs has shown to be encouraging sensitivity, for detecting several types of cancer, like colorectal cancer **(Gao et al. 2018)**, Gastric cancer **(Kotzev et al. 2018; Li et al. 2013)** and pancreatic cancer (**Meng et al. 2017; O'Brien et al. 2015).**

Lastly, may be the effect of low radiation on TMs behaviour presented as little increase from years to years, but a lot of investigation is needed to accurate the finding. It should take into account this study is retrospective, so the researcher could not neither consider the systematic errors of equipment nor use any different types of equipment through years, which, as a matter of fact, can affect the accuracy of the results.

Table (4.2) Percentages of each pattern of tumor markers during the years

Tumor markers	*Decrease %	* Increase %	*stable %
CEA **Normal range (0-5 ng/ml)**	9%	57%	34%
CA19-9 **Normal range(0-37 ng/ml)**	31%	46%	23%
CA125 **Normal range (0-35 ng/ml)**	37%	54%	9%

****Note that the increase, decrease and stable value was within normal range to all type of TM.**

Table (4.3) correlation between tumor markers according to smoking (T-test)

Tumor markers	smoking status	Mean	Std. Deviation	T	Sig
CEA	**Smoking**	1.71	0.84	2.88	0.01
	Not Smoking	1.21	0.59		
CA19-9	**Smoking**	5.99	6.07	0.39	0.70
	Not Smoking	5.47	4.73		
CA125	**Smoking**	11.14	4.54	0.77	0.45
	Not Smoking	10.12	5.37		

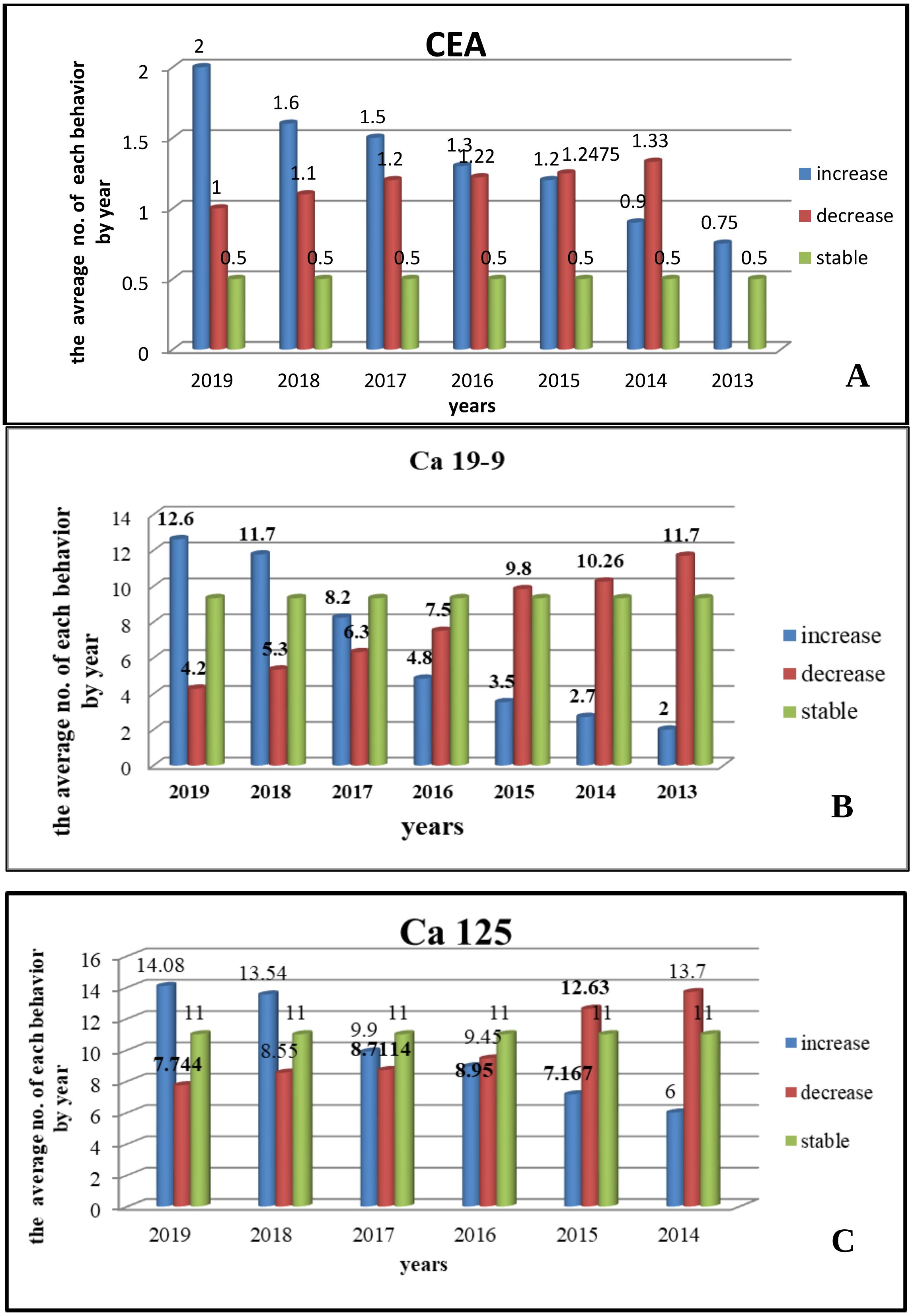

Figure 4.2 the average value for CEA, CA19-9 and CA125 for each pattern by the year.

4.4 Correlation between Tumor Markers and Independent Variables

Determining how different variables can affect TMs is vital since it can help to understand how TMs are affected by radiation, after isolating the effects of other variables. The following tables illustrate significant differences at the level of ($p \leq 0.05$) due to TMs effects according to independent variables such as the cumulative dose, Hospital location, and type of work. The researcher tested the hypotheses for each variable separately as follows:

4.4.1 The Cumulative dose & TMs:

The researcher divided the RWs into two groups according to cumulative dose. Group had a registered radiation dose about 1mSv or less, and second group above 1 mSv. Comparing their average means to each tumor markers. The independent-sample t-test is used, as shown in **table (4.4),** the result shows no significant mean difference according to cumulative dose. However, when reveal to average doses for each years from 2019, 2018, 2017, 2016, and 2015 with an annual average dose found to be at 0.50, 0.67, 0.77, 0.5, and 0.72 mSv, respectively. The maximum doses found to be 2.021, 4.519, 4.266, 2.679, 4.875 mSv, respectively, which means that the average dose for most RWs did not exceed the annual dose limit of 20 mSv for occupational workers. Although an enhancement in the field of protection makes the annual average dose decrease over the years of work, more noticeably in the last three years. Regular reading of the cumulative doses and carrying out TMs tests make more accurate observations on how radiation affects TMs or other tests that are done for RWs.

Finally, one of biggest concern in this study is informed the RWs about their doses, as seen in **figure (4.3),** where just *27%* answered correctly about their receiving dose, *15%* did not even know how much their dose was, and the rest of the workers, suspected a higher dose, rather than the dose they were actually exposed too. This perhaps illustrates why Palestinian RWs predict the worst from radiation, even if an exposure dose is within a limit. In the absence of a policy-officer in most Hospitals, no one reporting or following up on what may happen makes them confused about the monitoring system.

Table (4.4) correlation between tumor markers according to a cumulative dose (T-test)

Tumor markers	Annual Cumulative dose	Mean	Std. Deviation	T	Sig
CEA	less than 1msv	1.38	0.82	-0.59	0.56
	more than 1msv	7.42	6.40		
CA19-9	less than 1msv	11.34	5.11	-0.40	0.69
	more than 1msv	1.38	0.82		
CA125	less than 1msv	7.42	6.40	1.03	0.31
	more than 1msv	11.34	5.11		

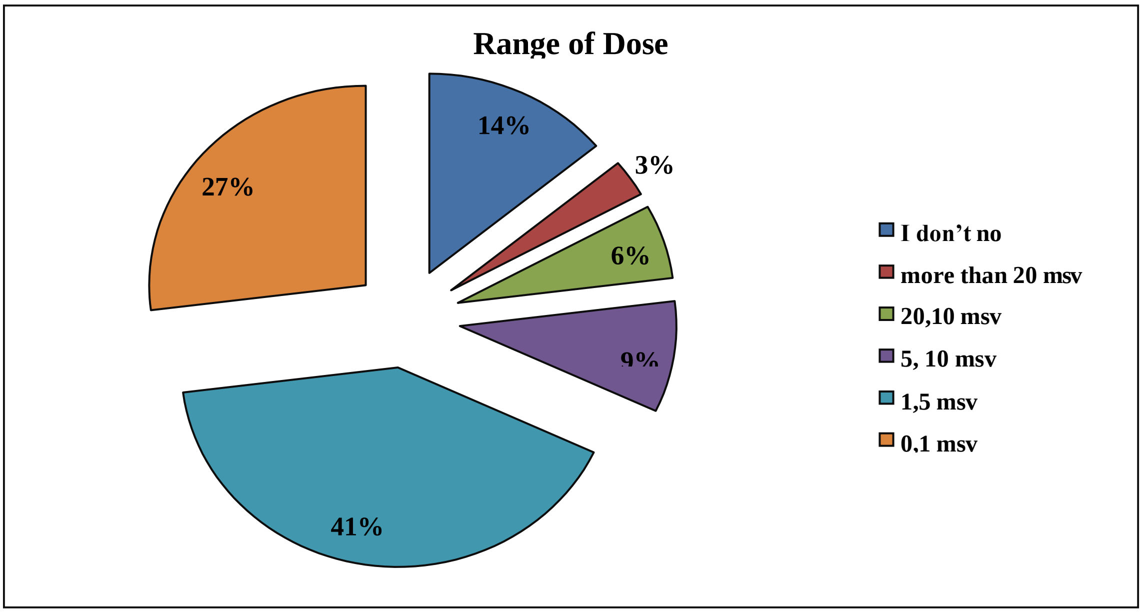

Figure (4.3) Percentages of technicians' answers about the doses of radiation they think receive annually.

4.4.2 Hospital location & TMs:

The researcher links an average for each TM with the Hospital location to figure out if the background radiation in West Bank is effective factor as mentioned in the previous study **(Taeb et al. 2014).** By using (One Way ANOVA) test, and when revered to **table (4.5)** the result shows that; there is no significant differences, according to the Hospital location. Perhaps the reason for this is because the background radiation in different Palestine cities is within global normal range around 2.4 mSv per year and that indicated in several previous studies **(UNSCEAR, 2008; Lahham et al., 2009; Houshia et al., 2012 ; Thabayneh & Jazzar 2012).**

Table (4.5) Correlation between tumor markers according to Hospital location (ONE-WAY ANOVA).

Domain	Source of variation	Sum of Squares	d.f	Mean Square	F	Sig.(P)
CEA	Between Groups	4.12	3	1.37	2.61	0.06
	Within Groups	32.63	62	0.53		
	Total	36.75	65			
CA19-9	Between Groups	93.37	3	31.12	1.09	0.36
	Within Groups	1764.18	62	28.46		
	Total	1857.55	65			
CA125	Between Groups	21.43	3	7.14	0.28	0.84
	Within Groups	1374.52	53	25.93		
	Total	1395.94	56			

4.4.3 Work type & TMs:

The researcher tried to find if there was a relationship between two groups of workers on different devices, the x-ray/CT group and the interventional group, and compare the means average to each tumor marker for each group. As shown in **table (4.6),** Furthermore, based on the results of the independent-sample t-test, the means of two groups were not significantly different. In fact, because the rotation system in the radiation department (no specific RW to any type of equipment), that benefits to distribute a dose while working with high dose procedures (like interventional) among RWs. According to the World Health Organization which reported "Where higher doses are possible, careful use of worker rotations will reduce the risks**" (World Health Organization 2003).**

Table (4.6) correlation between tumor markers according to type of work (T-test)

Tumor markers	type of work	Mean	Std. Deviation	T	Sig
CEA	**CT , x-ray**	1.35	0.72	-1.05	0.30
	Interventional	1.55	0.80		
CA19-9	**CT , x-ray**	6.51	6.48	1.39	0.17
	Interventional	4.68	3.22		
CA125	**CT , x-ray**	10.29	4.81	-0.50	0.62
	Interventional	10.96	5.29		

Chapter Five

Conclusions and Recommendations

5.1 Conclusions

the researcher believes this study contribute to ‘gap-filling’ in low doses radiation effects which is today a big concern because the effect of low radiation doses is difficult to notice and not long ago it just extrapolating from the high doses of radiation, all these facts demonstrate the importance of laboratory medical tests in assessing and monitoring the low doses in radiation worker.

Also, the results of this study show the CEA as TMs having the highest percentages of increase over years about 57% of the RWs have an increase in it. But do not forget that; all TMs did not increase beyond the normal range, also not shown any effected with cumulative dose. The effect of radiation maybe presented as little increase from years to years. the increase is the most pattern that TMs is behaved, but more investigation are need like repeat this study and comparing this group of worker with another type of workers, to understand if this increase that have noticed here come from radiation or not . The Insufficient data on TMs and irregularity in carrying out tests over years makes observing the radiation effects on TMs tests inaccurate. The retrospective study causes the researcher to not take into account equipment errors.

The results of this study showed that 73% responded that their tests were not followed by anyone. Additionally, 91% admit that no action was taken in the event of an abnormal results appear. And just 27% of RWs know about their received doses. all of this lead to conclude ; there is need to a policy officer to follow what is happening, or what should be done in the event of a test result being abnormal.

5.2 Recommendations:

1. Hiring a radiation safety officer whose responsibility is organizing TM tests in hospitals regularly, follow-up and taking the necessary procedures with the worker in case of any abnormal results.

2. Repeat this study after a few years to reach real facts, concerning what radiation actually does to our body.

3. The rotation system is not just for training the RWs to work with different types of procedures but also to help distribute high doses to all workers, thus, making everyone in an safer environment.

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Appendix 1: Questionnaire

The researcher Areej Najib Dahdol, a student in the Master of Medical Imaging Technology Program, Al-Quds University, and this study was conducted for scientific research in the service of the community,

This questionnaire was designed to examine the tests (tumor markers) for radiation workers, it's includes several questions and themes about the research objectives, and will correlated to TMs record and exposure dose record, the information received from it will be treated for research purposes only and strictly confidential.

Thank you for your cooperation

Social and demographic factors

- Age: ( )
- Place of living: ( )

Please answer the following questions by circle the appropriate answer:

1. Sex

A. Male

B. Female

2. Smoking status:

A. Smoker

B. Non-smoker

3. Years of working:

a. Less than 5 years

B. 5- 10 years

C. 10 years and over.

Academic level

a. Diploma degree.

b. Bachelor's degree.

c. Postgraduate.

5. Which of the following devices is used in your field (Note: if you are working on more than one device choose more than one answer):

A. CT scanner

B. X-Ray Radiography

C. Dental X-ray

D. Interventional Radiology

E. Nuclear Radiation (Gamma Camera, SPECT, PET)

F. Fluoroscopy

G. Radiation therapy

H. Angiography

Radiation Knowledge and Prevention: Section II

6. Have you heard of a laboratory test called tumor marker?

A. Yes

B. No

7. How many times have you undergone a tumor marker?

A. Not once

B. Every 6 months

C. Once a year

D. Every two years and more

E. I do not know

8. The cumulative radiation dose you receive as an ionizing agent (yearly) ranges

from:

1. 0- 1 mSv

2. 1-5mSv

3. 5-10mSv

4. 10-20mSv

5. More than 20mSv

9. Check the appropriate answer intended for tumor marker tests

Items	Yes	No	I don't know
Are you informed about your test result no matter what it is?			
Is this test saved in the technical records?			
Are the test results followed by responsible people?			
Are you carrying out this test regularly?			
Do you think radiation exposure may affect the results of this test?			
Is there any action taken by officials if there is a variation in the result?			

10. What action (if any) is taken by the officials if there is a change in the results of this examination:

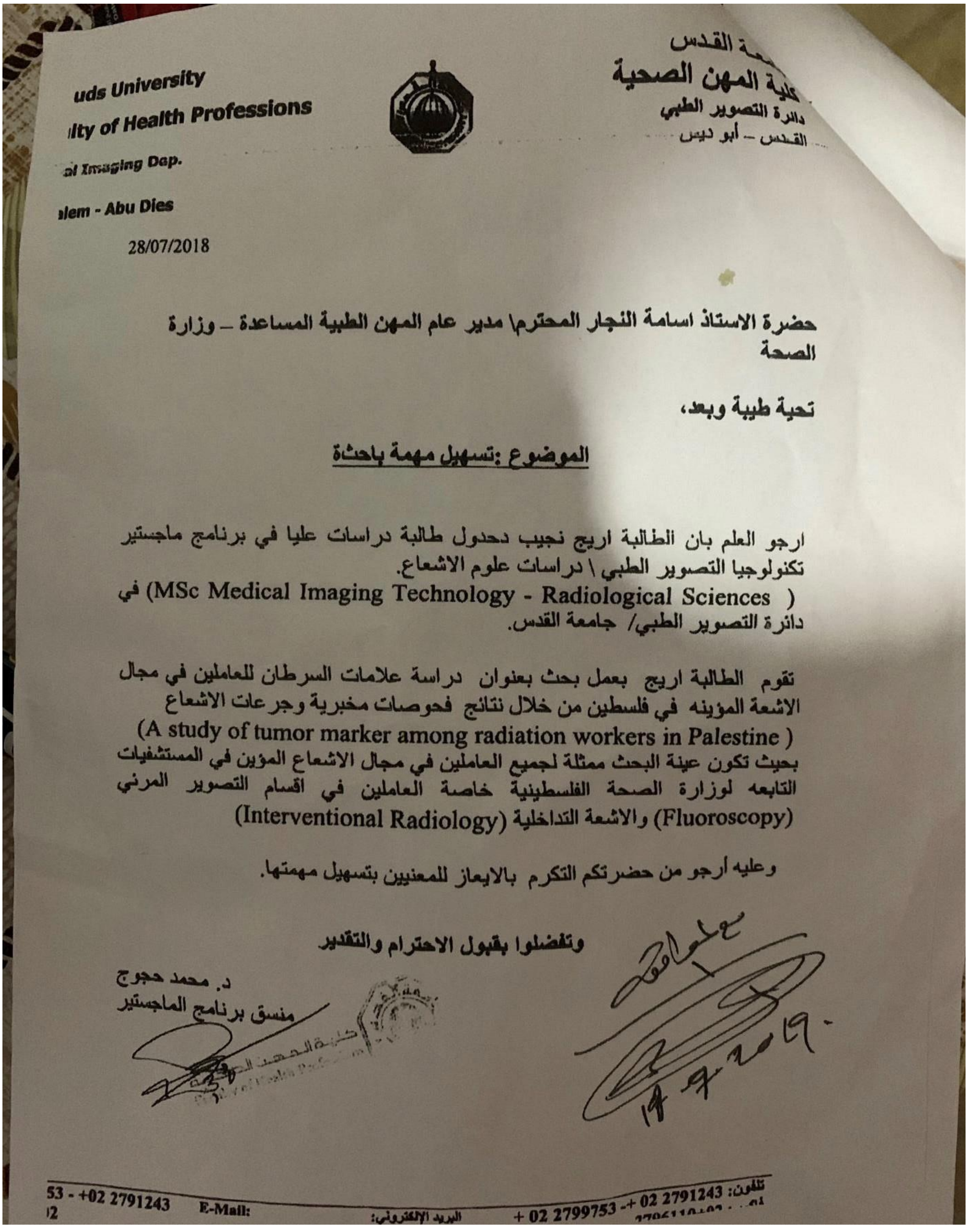
……………………………………………………………………………

11. Do you have any chronic diseases or have you ever had any diseases?

………………………………………………………………………………………………..

Thank you for your cooperation in answering these questions, this will help us to better serve you.

Appendix 2: Approval to facilitate the task for students from the Palestinian Ministry of Health



uds University
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al Imaging Dep.
lem - Abu Dies

...عة القدس
كلية المهن الصحية
دائرة التصوير الطبي
القدس – أبو ديس

28/07/2018

حضرة الاستاذ اسامة النجار المحترم\ مدير عام المهن الطبية المساعدة – وزارة الصحة

تحية طيبة وبعد،

الموضوع :تسهيل مهمة باحثة

ارجو العلم بان الطالبة اريج نجيب دحدول طالبة دراسات عليا في برنامج ماجستير تكنولوجيا التصوير الطبي \ دراسات علوم الاشعاع.
في (MSc Medical Imaging Technology - Radiological Sciences)
دائرة التصوير الطبي/ جامعة القدس.

تقوم الطالبة اريج بعمل بحث بعنوان دراسة علامات السرطان للعاملين في مجال الاشعة المؤينه في فلسطين من خلال نتائج فحوصات مخبرية وجرعات الاشعاع
(A study of tumor marker among radiation workers in Palestine)
بحيث تكون عينة البحث ممثلة لجميع العاملين في مجال الاشعاع المؤين في المستشفيات التابعه لوزارة الصحة الفلسطينية خاصة العاملين في اقسام التصوير المرئي (Fluoroscopy) والاشعة التداخلية (Interventional Radiology)

وعليه أرجو من حضرتكم التكرم بالايعاز للمعنيين بتسهيل مهمتها.

وتفضلوا بقبول الاحترام والتقدير

د. محمد حجوج
منسق برنامج الماجستير

14-7-2019

53 - +02 2791243 E-Mail: البريد الالكتروني: + 02 2799753 -+ 02 2791243 :تلفون

State of Palestine
Ministry of Health
General Directorate
of Paramedical Services

دولة فلسطين
وزارة الصحـــــة
الإدارة العامة
للخدمات الطبية المساندة

الاخ الدكتور حمدي النابلسي المحتـــــــــرم
ق.أ مـــــدير عام الادارة العامة للمستشفيات
الأخ الدكتور أحمد البيتاوي المحتـــــــرم
مـــــــــــــدير مجمع فلسطين الطبـــي

GDPS- 649 ص
23/7/2019

الموضوع: تسهيل مهمة

تحية طيبة وبعد،،،

نرجو تسهيل مهمة الطالبة اريج نجيب دحدول – ماجستير تكنولوجيا التصوير الطبي من جامعة القدس لعمل بحث بعنوان دراسة علامات السرطان للعاملين في مجال الاشعة المؤينة في فلسطين من خلال نتائج فحوصات مخبرية وجرعات الاشعاع لذا يرجى تسهيل مهمتها مع الموظفين العاملين في اقسام الاشعة في المستشفيات، مع العلم بأنه سيتم التعامل مع كافة المعلومات بسرية تامة وتستخدم لأغراض البحث العلمي فقط.

وتفضلوا بقبول فائق الاحترام،،،

أخوكم
أسامة النجار
مدير عــــــام
الادارة العامة للخدمات الطبية المساندة

Ministry of Health – Ramallah
Ministry of Health - Nablus

TelFax: 022964402 :تلفاكس
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وزارة الصحة – رام الله
وزارة الصحة – نابلس

Appendix 3: The Published Article

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Assessment of Low Doses Radiation Effects Using Tumor Markers Among Palestinian Radiation Workers

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Abstract

Understanding the impact of radiation on occupational workers has been a huge concern; particularly when it comes to cancer, which is considered a stochastic effect from radiation. This paper aims at investigating the effects of low radiation doses on tumor markers tests among Radiation Workers (RWs). It also aims at demonstrating the effect of independent variables, such exposed dose, smoking status, and the type of work on tumor markers. The researchers reviewed the collected database of tumor marker tests in four Governmental Hospitals between the period (2013- 2019) in order to trace the patterns of tumor marker over the years. The exposed dose record was taken from the Energy Department. Additionally, a questionnaire was distributed to acquire correlated independent variables with tumor markers records and 78 RWs participated in this study. Results indicated that after several years of tracing tumor markers, they all tend to increase in a normal range. Significantly, the Carcinoembryonic antigen (CEA) has increased by approximately 57% in RWs. Moreover, the smoking workers have a statistically significant change in CEA. Finally, the study has not shown any relationship between the radiation doses and tumor markers. In conclusion, to the best of the researchers' knowledge, this is the first study to investigate the correlated tumor markers with low radiation doses among occupational worker. The researchers believe that these findings will contribute to 'gap-filling' in low dose effects, and demonstrate the importance of laboratory medical tests in prediction of low doses effect. However, further investigations are needed in order to achieve more accurate results.

Keywords: Low dose, Radiation workers, Tumor markers, Cancer, Stochastic effects, Retrospective.

Introduction

Occupational radiation workers (RWs) are more likely to receive low doses of radiation over a long period. The basic of low doses radiation effect is non-lethal mutations, with the biggest concern being the induction of cancer. This concern comes from the fact that some radiation risks are associated with dose by a linear, no-threshold model. In brief, linear means a proportional relationship between the dose and the risk. Additionally, any dose -no matter how small this does is-, which may cause some risks is called no-threshold (Calabrese and O'Connor, 2014). Furthermore, the study reported that cancer in RWs has significantly increased over the years (Choi et al., 2013).

Several recent studies have shown evidence of cancer among occupational worker. One study used human's peripheral blood lymphocytes to assess the DNA damage. Antioxidant status shows that the chronic low dose exposure is an unavoidable hazard, which would lead to an oxidative stress, increased genomic instability, and a rise in cancer among RWs (Siama et al., 2019). Moreover, the incidence of thyroid cancer rates is higher among Korean RWs than the general population (Lee et al., 2018; Lee et al., 2019). Another study on health risks shows an increase in all of skin lesions, orthopedic illness, cataract, hypertension, and hypercholesterolemia in cardiac catheterization workers (Andreassiet al., 2016). One study, which focused on reliable cancer mortality risks from a low-dose in a nuclear industry, showed an evidence of stochastic effects and statistical significance for lung cancers (Qu et al., 2018). Based on that, it is crucial to provide the population with more intensive and protective measures, safe development tools, and acceptable tests for the early detection of cancer (Schiffman et al., 2015).

Tumor biomarker is one of the most important tools, referred as a secreted molecule in the blood arising out of a tumor in case of cancer presence. Although the field of radiation detection shows that, an assessment of absorbed dose using a protein with gene expression, will be considered as a good biomarker

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of radiation, the insufficient sensitivity and specificity of tumor marker tests generate positive results, yet this does not necessarily indicate the presence of cancer. This means that additional procedures, such as biopsy, x-rays, or etc., are needed in conjunction with these tests. (Sahoo, 2018; Kayaba, 2003; Rana et al., 2010).

Some tumor markers, such as CEA glycoprotein, are used for screening the elevated levels found in colorectal, breast, lung, or pancreatic cancer and, in smokers (Bhatt et al., 2010). However, it has special sensitivity among markers for colorectal cancer (Gao et al. 2018). Another marker is Cancer Antigen 19-9, commonly used for pancreatic cancer (Scarà, 2015). While the regular CA19.9 measurements show an improvement in early detection of biliary tract cancer, the last one will included in this study is a Carbohydrate Antigen 125, a tumor marker for ovarian cancer. However, study shows that a combination of CA125 and human epididymis protein 4 (HE4) improves the sensitivity and specificity of ovarian cancer (Wannhoff, 2019).

On the other hand, several studies have reported that multiple markers are more useful in the detection of some cancers. Some other studies reported that the combination of CA 19-9, CEA, and other markers will increase sensitivity and specificity in Gastric cancer. Moreover, other studies have shown that the combination contributes to diagnoses and prediction of pancreatic cancer. The combination of CA19-9 and CA125 has shown to encourage sensitivity for pancreatic cancer (Kotzevet al., 2018; Li et al., 2013; Meng et al., 2017; O'Brien et al., 2015).

Similarly, the impact of occupational radiation on some tumor markers, and the effect of high background radiation on them have been studied. A Study in 2019 in the field of Biomarkers indicates that, levels of serum 8-OHdG which is a biomarker resulted in oxidative stress, were found to be significantly higher in interventional RWs (Gao et al., 2019). Likewise, a study in Ramsar (Iran) has shown that there is significant alteration in Cyfra 21, CEA, and Tag 72 levels due chronic exposure to high background radiation (Taeb et al., 2014).

The researchers believe that studying and investigating tumor markers might help highlight low radiation effects, especially cancer, among the workers are exposed to chronic low doses.

Materials and Methods

Study Participants

For the study approval, Al-Quds University sent letters including the purpose of the study to the Ministry of Health (MoH). Official permission was obtained to visit the Hospitals and distribute the questionnaires in addition to facilitate data collection procedures. A one-page participants' Consent Form was attached to the questionnaire. The researchers gave total freedom to accept or reject participation in this research. (78) RWs participated. Workers with diseases, such as (hepatic disorders, diabetes or any other kind of disease), were excluded for the accuracy of the results. A worker with diagnostic modalities that did not utilize ionizing radiation (like MRI, U/S) was also excluded.

Data Collection

After Institutional Review Board Approval, the researchers retrospectively reviewed a collected database of tumor marker tests in four Governmental Hospitals between 2013 and 2019 to trace the patterns of TM tests over the years. Commercial Architect kits had been used to measure the serum levels of CA125, CEA, and CA19.9 tumor markers. The test records are distributed as follows, 42 records of CEA, 45 records of CA 19.9, and 35 records of CA125 conducted over the years of the study. Independent variables, such as smoking status and the type of work, were reached and obtained by the distributed questionnaire, while the dose recorded was taken from a database of the Energy Department.

Statistical Data Analysis

Collected data were analyzed by using SPSS, Version 22. Student's t-test was used for testing the equality of the means in the groups. P-value <0.05 was considered significant. Descriptive statistical analysis was used to determine the tumor marker behavior along several years.

Results and Discussion

Assessment of Tumor Markers Test through Years

At the beginning, the researchers tried to study whether the exposed dose had an effect on TMs by dividing RWs into two groups according to the exposed dose. One group had a registered radiation dose of about 1mSv or less, while the second had over 1 mSv. Then, the researchers compared their average means to each tumor markers. As noted, the average doses for each year from 2019, 2018, 2017, 2016, and 2015 with an annual average dose found to be at 0.50, 0.67, 0.77, 0.5, and 0.72 mSv, respectively. The maximum doses were found to be 2.021, 4.519, 4.266, 2.679, 4.875 mSv, respectively. This means that the average dose for most RWs did not exceed the annual dose limit of 20 mSv for occupational workers.

As shown in Table 1, the independent-sample t-test is used to investigate whether the exposed dose had an effect on TMs. The result shows no significant mean difference according to the exposed dose. Actually, the irregular readings of the exposed doses make the results inaccurate. Therefore, the researchers decided to explore what is going to happen to the TMs through years of exposure to the radiation.

Accordingly, one of the most important questions in this study is: what happens to TMs test over several years of work in the Radiation Department? According to Table 2 which represents the percentages of how TM tests of RWs behave over the years (from 2013 to 2019), the TM test pattern is expressed by scale levels (decrease, increase, and stable). However, the unstable state is ignored due to an unclear behavior. In addition the average number of each behavior according to specific year is demonstrated in (Figures 1, 2, and 3), for each type of tumor markers separately. These figures show how the average value was for each tumor marker and its behavior from the first year

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Table 1. Statistically significant relationship between tumor markers according to an exposed dose (independent T-test).

Tumor Markers	Annual Exposure Dose	Mean	Std. Deviation	T	sig
CEA	less than 1msv	1.38	0.82	-0.59	0.56
	more than 1msv	7.42	6.40		
CA199	less than 1msv	11.34	5.11	-0.40	0.69
	more than 1msv	1.38	0.82		
CA125	less than 1msv	7.42	6.40	1.03	0.31
	more than 1msv	11.34	5.11		

Table 2. Percentages of the behavior patterns of tumor markers during the years.

Tumor markers		*Decrease	* Increase	*Stable
CEA Normal range (0-5 ng/ml)	Percent%	9%	57%	34%
CA199 Normal range(0-37 ng/ml)	Percent%	31%	46%	23%
CA125 Normal range (0-35 ng/ml)	Percent%	37%	54%	9%

**Note that the increase, decrease and stable value was within normal range to all type of TM.

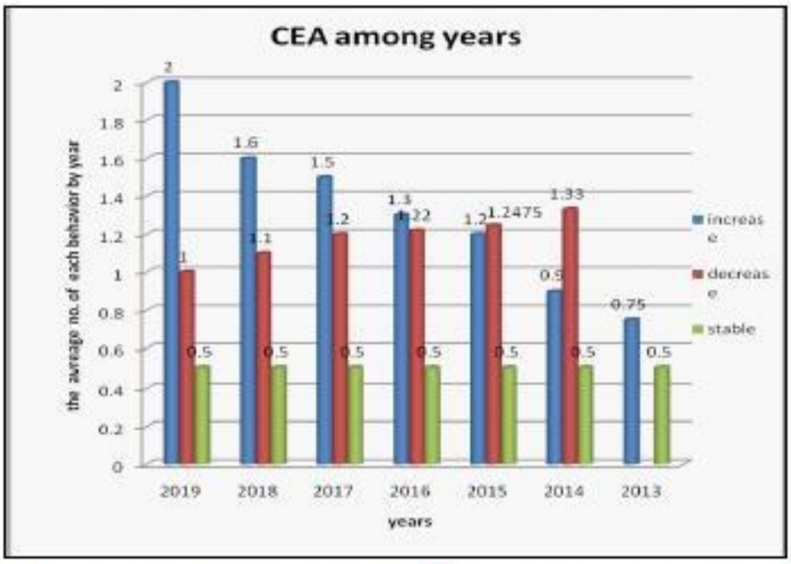

Figure 1. Demonstration of the average value for CEA behaviors by the year. The average CEA value was (0.75 ng/ml) in the first year (2013), which illustrates the average of the RWs who have an increase (which represent about 57% of the RWs, see table 2) and the average of increase became (2.0 ng/ml) in the last year (2019). This shows the rate of increase over the years. It is worth mention that this example applies to all behaviors.

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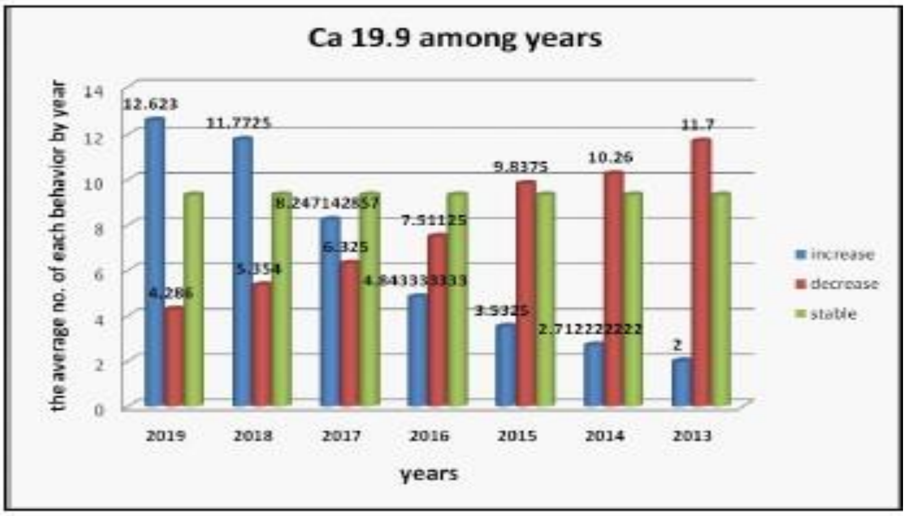

Figure 2. Demonstration of the average value for CA 19.9 behaviors by the year. The average value was (2 ng/ml) in the first year (2013), which illustrates the average of the RWs who have an increase (which represent about 46% of the RWs, see table 2), then the average of increase became (12.0 ng/ml) in the last year (2019). This shows the rate of increase over the years. It is worth mention that this example applies to all behaviors.

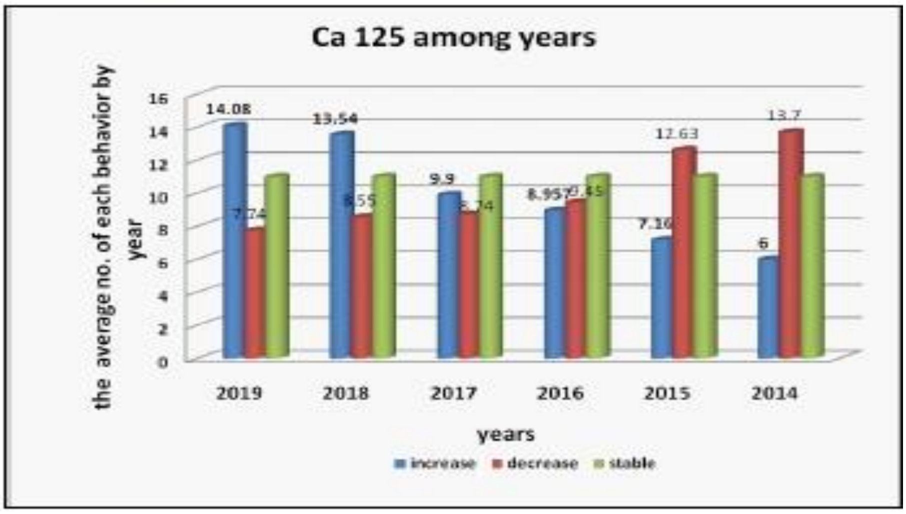

Figure 3. Demonstration of the average value for CA 125 behaviors by year. The average value was (6.0 ng/ml) in the first year (2014), which illustrates the average of the RWs who have an increase (which represent about 54% of the RWs, see table 2), then the average of increase became (14.0 ng/ml) in the last year (2019). This shows the rate of increase over the years. It is worth mention that this example applies to all behaviors.

Table 3. Statistically significant relationship between tumor markers according to smoking (Independent T-test).

Tumor Markers	smoking Status	Mean	Std. Deviation	T	sig
CEA	**Smoking**	1.71	0.84	2.88	0.01
	Non-smoking	1.21	0.59		
CA199	**Smoking**	5.99	6.07	0.39	0.70
	Non-smoking	5.47	4.73		
CA125	**Smoking**	11.14	4.54	0.77	0.45
	Non-smoking	10.12	5.37		

Table 4. Statistically significant relationship between tumor markers according to type of work (Independent T-test).

Tumor Markers	Type of Work	Mean	Std. Deviation	T	Sig
CEA	**CT , x-ray**	1.35	0.72	-1.05	0.30
	Interventional	1.55	0.80		
CA199	**CT , x-ray**	6.51	6.48	1.39	0.17
	Interventional	4.68	3.22		
CA125	**CT , x-ray**	10.29	4.81	-0.50	0.62
	Interventional	10.96	5.29		

to the last year.

As shown in Table 2, we found a 57% increase in CEA TMs but within the normal range of 0-5 ng/ml (Table 2, Figure 1). Only one RW had abnormal results in the CEA. This reminds us of the alteration occurrence in CEA levels in a high background radiation (Taeb et al., 2014). These findings may highlight CEA as the most sensitive TM to radiation, due to the highest percentage of increase among TMs, being more stable and having the lowest percentage of decrease over the years. The elevated CEA may appear in case of lung cancer as mentioned by Bhatt et al. (Bhatt et al., 2010). In fact, lungs are considered as one of the sensitive organs to radiation with a risk factor at 2.0 *10 -3 Sv-1 (Till and Grogan, 2008). Moreover, it is important to mention the effect of smoking in CEA (as will be discussed below), which may help in the interpretation of this increase. In any case, more investigation is needed to accurate the findings. However, CA-19.9 and CA125 have an increase of (46%) and (54%) within the normal range (figures 2 and 3) respectively. Additionally, there is a tendency for a decrease of (31%) and (37%), respectively, with a very low percentage of stability in CA-19.9 and CA125 as TMs. Overall, the increased pattern was the most behavior TMs have followed. This is despite the fact that, as mentioned in more than one study, the combination of TMs has shown to be an encouraging sensitivity, for detecting several types of cancer, such as colorectal cancer (Gao et al., 2018), Gastric cancer (Kotzev et al., 2018; Li et al., 2013), and pancreatic cancer. (Meng et al., 2017; O'Brien et al., 2015).

Lastly, the effect of low radiation on TMs behavior may have shown a little increase over the years, but a lot of investigation is needed to obtain results that are more accurate. It should be taken into account that this study is retrospective; therefore, the researchers have neither considered the systematic errors of equipment nor used any different types of equipment over the years, which, in fact, can affect the accuracy of the results.

The Effect of Tumor Markers by Independent Variables

The determination of how different variables can affect TMs is vital. It can help to understand how TMs are affected by radiation, after isolating the effects of other variables. The following tables illustrate significant differences at the level of ($p \leq 0.05$) due to TMs effects according to the independent variables, such as smoking status, and type of work. The researchers tested the hypotheses for each variable separately as follows:

Smoking & TMs

The researchers compared the average means to each tumor marker for the two groups of RWs, smokers and non-smokers. The independent-sample t-test is used (table 3),the results show that only the means of CEA concentration between other markers have significant differences (p=0.01). The significant differences were in favor of the RWs who are smokers, thus, coinciding with other studies that proved that smoking affect CEA markers (Bhatt et al., 2010; Nan et al., 2017). According to that, smoking may cause the effects of radiation on RWs to be worse. On the other hand; smoking does not affect the CA19-9 & CA125. This was suspected because smoking is not considered as an important factor in these markers, according to previous studies.

Work type & TMs

The researchers tried to find if there was a relationship between the two groups of workers who work on different devices, the x-ray / CT group and the interventional group. They conduct this by comparing the mean averages to each tumor marker for each group. Based on the results of the independent-sample t-test (table 4), the means of the two groups were not significantly different. This may be attributed to the rotation system in the Radiation Departments (there is no specific RW

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to any type of equipment). It benefits to distribute a dose while working with high dose procedures (like interventional) among RWs. World Health Organization (WHO) reported, "Where higher doses are possible, careful use of worker rotations will reduce the risks" (World Health Organization, 2003).

Conclusion

The researchers believe that these findings will contribute to 'gap-filling' in low dose effects, and demonstrate the importance of laboratory medical tests in the prediction of low doses effect. The effect of radiation may be presented as little increase from years to years, as the increase is the most pattern that TMs is behaved. However, further investigation is still needed. It is important to repeat this study after few years in order to understand how radiation affects our bodies. Smoking workers have a significant difference in CEA tumor marker. A recommendation must be issued to reduce smoking when working with radiation because it might make the effects of the radiation worse for RWs. The rotation system does not only aim to train RWs to work with different types of procedures, but also helps distribute high doses to all workers, thus, making everyone in a safer environment. Surely this does not prevent tests from being inaccurate for the early detection of CA as mentioned earlier in previous studies. According to that, workers in this field may need more accurate tests, or we may consider radiation to be safer than what we really think. In light of this, studying tumor markers helps policymakers decide if they should approve policies to decrease the irradiation of occupational radiation work, or recommended better laboratory tests that monitor the chronic low doses effect on RWs.

Finally, the researchers state that due to chronic low doses of radiation received by occupational RWs, an effective remedial action program to protect this population should be of the highest concern.

Conflict of Interest

The authors declare no conflict of interest.

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الملخص:

اعداد اريج دحدول

إشراف :د محمد حجوج

تحليل تأثرعلامات الورم بعد التعرض للإشعاع بين عمال الإشعة في فلسطين

الهدف: كان الهدف من هذا العمل هو التحقق من أثر الجرعات المنخفضة من الإشعاع على فحوصات علامات الورم. وأيضاً تقييم السياسة التي تقوم بتنظيم إجراء هذه الفحوصات بين العاملين في أقسام الاشعة، ودراسة اثر المتغيرات المستقلة مثل الجرعة التراكمية ، وموقع المستشفى، ونوع العمل على علامات الورم.

الطريقة: قد راجع الباحث قاعدة البيانات لأخذ السجلات لفحوصات علامات الورم في أربعة مستشفيات حكومية بين سنة 2019-2013 ، وذلك لمتابعة أنماط علامة الورم على مر السنين. وتم أخذ سجلات الجرعات التراكمية من وحدة الطاقة في وزارة الصحة الفلسطينية . وقد شارك 78 عاملًا في مجال الإشعاع ، وتم توزيع استبيان لربط المتغيرات المستقلة بسجلات علامات الورم ، بالإضافة لتقييم السياسة المتبعة لإجراء هذه الفحوصات بين العاملين في اقسام الاشعة.

النتائج: بعد عدة سنوات من متابعة عالمات الورم ، تميل جميع علامات الورم الى الزيادة في المعدل الطبيعي, خاصة (CEA) حوالي 57 ٪ من العاملين بالاشعاع لديهم زيادة في هذا النوع من علامات الورم ، العمال المدخنين كان لديهم تغير ذات دلالة إحصائية في (CEA) . كما لم تظهر الدراسة أي علاقة بين جرعات الاشعة وعلامات الورم. بينما أظهر مقياس مستوى المعرفة للسياسة أن 73٪ من العاملين أجابوا أنه لا يوجد أحد مسؤول عن متابعة نتائج هذه الفحوصات ، وقد أقر 91 ٪ أنه لا يوجد إجراء متخذ في حال ظهور نتيجة غير طبيعية لديهم..

الخلاصة: حتى الأن كانت جميع نتائج فحوصات علامات الورم ضمن القيم الطبيعية, حتى لو كانت تميل لزيادة طفيفة من سنة لأخرى, ولكن هذا لا يثبت شيء دون تكرار هذه الدراسة ومقارنة العاملين في مجال الأشعة المؤينة مع عمال في مجلات أخرى, لكي نفهم ما إذا كانت هذه الزيادة التي لوحظت هنا في هذه الدراسة تأتي من الإشعاع أم لا. علاوةً على ذلك ،أيضاً تسليط الضوء على دور المسؤول عن مراقبة و تنفيذ هذه الفحوصات ومتابعة ما يحدث في نتائج فحوصات العاملين في مجال الإشعاع.