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# Les facteurs de risque de cancer du sein chez les femmes marocaines dans la région Fès, Maroc

Mohamed Khalis

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**Les facteurs de risque de cancer du sein chez les femmes marocaines dans la région Fès, Maroc**

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## **Résumé**

### **Introduction :**

Le cancer du sein est le cancer le plus fréquent chez la femme dans le monde. Au Maroc, comme dans de nombreux pays en voie de développement, l'incidence du cancer du sein a considérablement augmenté ces dernières années. Le rôle des facteurs de risque reconnus et suspectés dans la survenue du cancer du sein est peu étudié au Maroc. L'objectif principal de cette thèse était de déterminer les principaux facteurs de risque du cancer du sein chez les femmes marocaines dans la région de Fès- Maroc.

### **Méthodes :**

Ce travail porte sur les données de deux études cas-témoins réalisées dans la région de Fès-Maroc : l'étude "Fez Breast Cancer Study" (2014-2015) incluant 237 cas et 237 témoins appariés sur l'âge, et l'étude "BreCaFez Study " (2016-2017) incluant 300 cas et 300 témoins appariés sur l'âge et le milieu de résidence. Des informations détaillées sur les facteurs de risque du cancer du sein ont été recueillies au cours d'entretiens en face-à-face. Les odds ratios et leurs intervalles de confiance à 95% ont été estimés à partir de régressions logistiques, en ajustant sur les variables de confusion.

### **Résultats :**

Nos résultats montrent que (1) l'âge précoce de la ménarche et la nulliparité étaient significativement associés à une augmentation de risque de cancer du sein, tandis que l'âge précoce à la première grossesse à terme est associé à une diminution de ce risque ; (2) un score de mode de vie sain élevé était associé significativement à une réduction du risque de cancer du sein chez les femmes de notre population ; (3) un excès d'adiposité abdominale et une forte évolution de trajectoire de la silhouette étaient associés à une augmentation de risque du cancer de sein chez les femmes en pré- et en postménopause. En revanche, une large silhouette à l'enfance (6–11 ans) était associée à une diminution significative de risque de cancer du sein chez les femmes en préménopause et à la limite de la signification statistique chez les femmes en postménopause ; (4) les femmes ayant travaillées dans certaines professions du secteur de l'agriculture, en particulier celles employées comme ouvrière agricole, avaient un risque élevé de cancer du sein, une augmentation significative de ce risque en fonction de la durée de l'emploi a été également observée.

### **Conclusion :**

Ce travail suggère l'existence d'associations entre certains facteurs de risque et la survenue de cancer du sein chez les femmes de notre région. Les résultats de nos études peuvent orienter les mesures et les activités de prévention de cancer du sein dans notre pays. Par ailleurs, des études à plus grande échelle sont nécessaires pour confirmer et compléter nos résultats.

**Mots-clés :** Cancer du sein ; Facteurs de risque ; Epidémiologie ; Etude cas-témoins ; Maroc

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# Breast cancer risk factors among Moroccan women in the Fez region, Morocco

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## Abstract

### Introduction

Breast cancer is the most common cancer among women worldwide. In Morocco, as in many countries that are either developing or in epidemiological transition, breast cancer incidence rates have clearly risen. Numerous risk factors for female breast cancer have been identified in the literature, but their role in breast cancer among Moroccan women remains poorly documented. The purpose of this doctoral work was to investigate the association between several risk factors and breast cancer among Moroccan women in the Fez region, Morocco.

### Methods

Our analyses were based on data from two case controls studies conducted in the Fez region, Morocco: "Fez Breast Cancer Study" (2014-2015) including 237 cases and 237 age-matched controls, and the "BreCaFez Study" (2016-2017) including 300 cases and 300 controls matched by age and area of residence. Detailed information on various risk factors of breast cancer were collected through face-to face interviews. Odds ratios and 95% confidence intervals, adjusted for potential confounders were estimated by using logistic regression models.

### Results

Our findings suggest that (1) Early menarche and nulliparity were significantly associated with an increased risk of breast cancer among women of our population, whereas an early age at first full-term pregnancy was associated with a significantly decreased risk of breast cancer. (2) High healthy lifestyle index scores were associated with decreased risk of breast cancer in Moroccan women included in our study. (3) Central adiposity and body shape trajectory were positively associated with breast cancer risk in both pre- and post-menopausal women; whereas, a significant inverse association was observed between silhouette at young ages (6-11 years) and BC risk for premenopausal women and a borderline significant inverse association for postmenopausal women. (4) Women employed in specific agricultural occupations, particularly those who worked as crop farm laborers, had an elevated risk of breast cancer compared to those who never worked in these occupations and the risk increased with duration of employment.

### Conclusion

Our results showed the association between some risk factors and breast cancer among women in our region. It identified some susceptible groups at high risk of breast cancer. Preventive interventions and screening should focus on these groups as a priority. However, our findings should be confirmed in larger, multicenter studies.

**Keywords:** Breast cancer; Risk factors; Epidemiology; Case-control studies; Morocco

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## Valorisation scientifique

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#### *b. Articles en révision*

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#### *c. Article en préparation*

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### 2. Communications scientifiques

#### *a. Communications scientifiques sous forme de présentation orale*

**Khalis M**, El Rhazi K, Chajes V, Huybrechts I, Rinaldi S, Charaka H, Mellas N, Nejjari C, Romieu I, Soliman AS, Charbotel B. **Body size and the risk of breast cancer: Findings from a case-control study in Morocco**. The American Public Health Association (APHA)'s 2018 Annual

Meeting & Expo. Nov. 10–14, 2018, San Diego, USA.  
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*b. Communications scientifiques sous forme de poster*

**Khalis M**, Chajes V, Moskal A, Biessy C, Huybrechts I, Rinaldi S, Dossus L, Charaka H, Mellas N, Nejjari C, Soliman AS, Charbotel B, Romieu I, El Rhazi k. **Association between Five Lifestyle Habits and Breast Cancer Risk: Results from a case-control study in Morocco.** The European Congress of Epidemiology. July 4-6, 2018, Lyon, France.

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## Liste des abréviations

AICR	American Institute for Cancer Research
CHU	Centre Hospitalier Universitaire
CIRC	Centre International de Recherche sur le Cancer
CITP	Classification Internationale Type des Professions
ET	Écart-type
FAO	Food and Agriculture Organization
FFQ	Food Frequency Questionnaire
GCO	Global Cancer Observatory
GPAQ	Global Physical Activity Questionnaire
HCP	Haut-Commissariat au Plan
IMC	Indice de Masse Corporelle
IC	Intervalle de Confiance
IRC	Institut de Recherche sur le Cancer
INO	Institut National d'Oncologie
LMIC	Low-income and middle-income countries
MET	Metabolic equivalent
NACE	Nomenclature statistique des Activités économiques dans la Communauté Européenne
OR	Odds Ratio
ONG	Organisations Non Gouvernementales
CIRIHA	Centre d'Information et de Recherche sur les Intolérances et l'Hygiène Alimentaires
WCRF	World Cancer Research Fund International

## Chapitre I : Introduction

### 1. Transition démographique, épidémiologique et nutritionnelle au Maroc

A l'instar de nombreux pays émergents et en développement, le Maroc a vécu une transition démographique, socioéconomique, épidémiologique, et nutritionnelle au cours des dernières décennies. Cette transition s'est accompagnée d'une augmentation du nombre des sujets âgés, des taux d'urbanisation, d'un changement dans le style de vie et des habitudes alimentaires de la population Marocaine. Ainsi, elle a donnée naissance à une nouvelle situation épidémiologique caractérisée par l'émergence des maladies non transmissibles et des pathologies chroniques et dégénératives.

La transition démographique a commencée au Maroc à partir des années soixante. Le début de cette transition a été caractérisé par une baisse considérable de la mortalité, entraînant un accroissement rapide de la population avec un maintien de taux élevés de la fécondité, avant que ces derniers se baissent dans un deuxième temps.

Les taux de mortalité spécifique et globale ont connu une baisse très importante, grâce aux progrès médicaux, mesures de santé publique, éducation sanitaire et programmes de vaccination. En effet, le taux brut de mortalité est passé de 20,8‰ à 5,6‰ entre 1960 et 2010 [1,2]. La baisse de la mortalité infantile a été particulièrement forte, avec une chute de 149 décès pour 1000 naissances vivantes en 1962 à 30,2 ‰ en 2010 [2,3]. En conséquence, l'espérance de vie à la naissance a augmenté d'une manière considérable, elle est passée de 47,0 ans en 1962 à 74,8 ans en 2010, soit un gain de durée de vie moyenne d'environ 28 ans [1,4].

Parallèlement et à partir des années soixante-dix, le Maroc a connu une baisse très importante de la fécondité. L'indice synthétique de fécondité a baissé de 7,2 enfants par femme en 1962 à 2,2 enfants par femme en 2014 [1,2]. Ce recul remarquable de la fécondité s'expliqué principalement par l'accès croissant des femmes au marché du travail, le recul de l'âge au mariage, l'usage massive des moyens contraceptifs et l'adoption d'une politique nationale de planification familiale (programme national de planification familiale) [1,3].

Ainsi, le Maroc voit un grand changement dans sa pyramide des âges, avec une base qui se rétrécit de plus en plus suite à la baisse de la fécondité, et à l'inverse, un sommet qui s'élargit progressivement à cause de l'augmentation de l'espérance de vie et du nombre de personnes âgées.

A côté de cette dynamique démographique, le Maroc a connu également une très forte urbanisation. En effet, le taux d'urbanisation est passé de 29,1% en 1960 à 60,3% en 2014 [1]. Le Haut-Commissariat au Plan (HCP) explique cette évolution par l'accroissement démographique naturel et par l'exode rural, la création de nouveaux centres urbains et l'extension des périmètres urbains des villes [1]. Par ailleurs, dans les pays en voie de développement, l'urbanisation de la population est responsable en partie de la dégradation de l'environnement et du changement de style de vie des populations [5,6].

### ***Transition épidémiologique***

Depuis les années quatre-vingts, le Maroc vit une transition épidémiologique dite de la "double charge", où les maladies non transmissibles, telles que le diabète, le cancer, l'obésité, et les maladies cardiovasculaires viennent s'ajouter aux maladies infectieuses et parasitaires.

Malgré les efforts fournis pour l'amélioration des conditions de vie et d'hygiène de la population ainsi que pour l'accès aux soins de santé primaires, les maladies transmissibles représentent, encore environ 30 % de la charge de morbidité globale [2]. Certaines de ces maladies étaient et demeurent à ce jour un véritable problème de santé publique au Maroc [7]. À titre d'exemple, 30 897 nouveaux cas de la tuberculose ont été enregistrés au Maroc en 2017, avec un taux d'incidence d'environ 88 pour 100 000 personnes [8]. En outre, les maladies non transmissibles constituent une grande partie de la charge de morbidité globale au Maroc, ils représentent environ 60% de la charge de morbidité globale [2]. De plus, les décès par maladies non transmissibles sont 5,7 fois plus importants que les décès par maladies transmissibles [9]. En 2010, les maladies cardiovasculaires, les tumeurs, et les maladies endocriniennes, nutritionnelles et métaboliques, étaient responsable de 18,6%, 7,1% et 4,0 des causes de décès au Maroc, respectivement [9]. Le cancer du sein est un exemple de maladies chroniques qui représentent un fardeau important pour la santé au Maroc de point de vue de la morbidité et la mortalité. Par ailleurs, les accidents de la voie publique et les traumatismes sont responsables d'environ 10% de la charge de morbidité globale.

### ***Transition alimentaire***

La transition démographique et la transition épidémiologique s'accompagnent habituellement d'un changement dans le style de vie incluant les habitudes alimentaires, et par conséquent l'apparition de surpoids et d'obésité et l'augmentation de la prévalence de certaines maladies chroniques.

Au Maroc, la transition alimentaire a été marquée par le passage d'une alimentation traditionnelle, à base de céréales et de légumineuses, à une alimentation riche en produits d'origine animale et en sucres, et tend à devenir excessive par rapport aux besoins énergétiques d'une vie sédentaire [10,11]. Ce changement s'est également accompagné de l'augmentation de la consommation de fast-foods et de produits industrialisés, qui sont potentiellement impliqués dans la survenue de différentes maladies chroniques incluant le cancer. Par ailleurs, le rythme de ce changement est caractérisé par une grande disparité au niveau national, ainsi qu'entre milieux de résidence et classes socio-économiques.

Le Maroc à l'instar d'autres pays de la région méditerranéenne s'éloigne du régime alimentaire méditerranéen tel que prédéfini dans la littérature et qui est considéré comme étant un modèle de régime alimentaire sain au profit d'un autre régime alimentaire, plus occidental et moins sain [10,12].

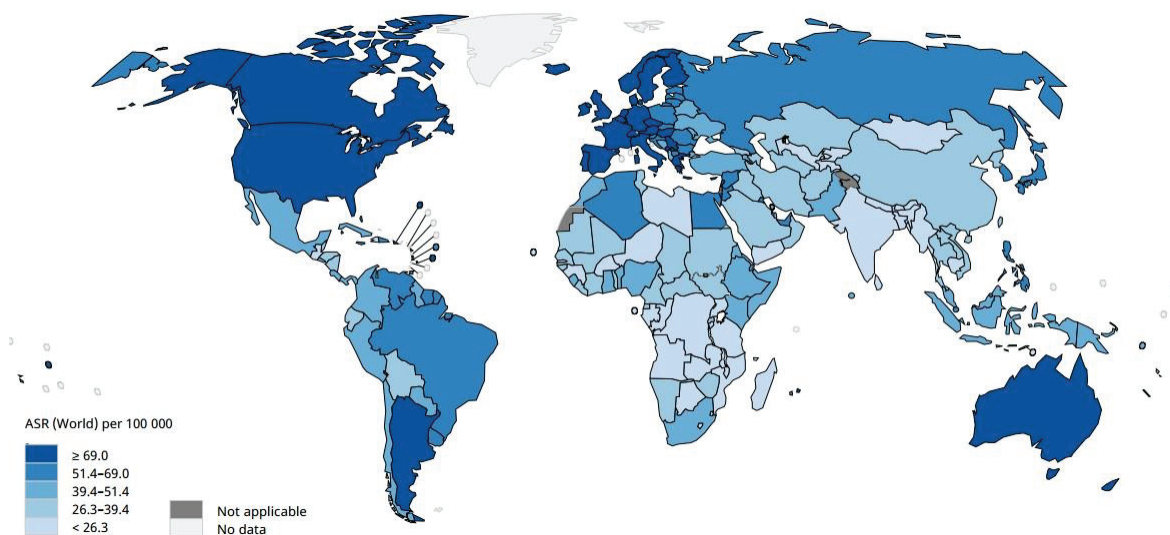
## 2. Epidémiologie descriptive du cancer du sein

### 2.1. Dans le monde

#### 2.1.1. Incidence du cancer du sein

Le cancer du sein est le cancer le plus fréquent chez la femme dans le monde [13]. Environ 2,08 millions de nouveaux cas de cancer du sein sont diagnostiqués à travers le monde en 2018, Il représente 24,2 % (soit environ un sur quatre) des nouveaux cas de cancers féminins, et 11,6% de l'ensemble des cancers (tous sexes confondus) [13].

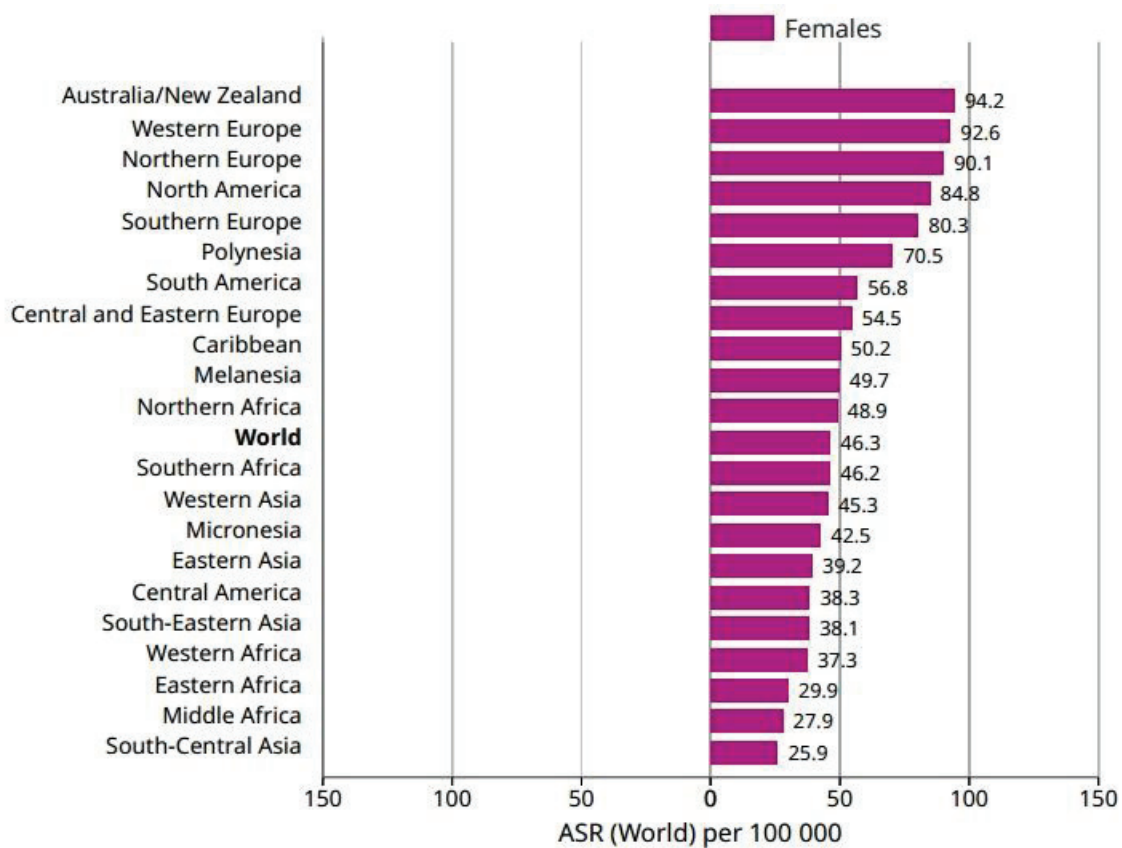
Les taux d'incidence varient beaucoup d'une région du monde à l'autre (Figure 1), avec un rapport qui peut aller de 1 à 4 entre les pays généralement développés à forte incidence et les pays en voie de développement à relativement faible incidence [14]. Actuellement, les taux d'incidence les plus élevés sont observés en Australie, Nouvelle Zélande, au Nord et à l'Ouest de l'Europe, ainsi qu'en l'Amérique du Nord. Les taux intermédiaires sont observés en Europe Centrale et Orientale, et au Nord et au Sud de l'Afrique et les taux les plus bas au Centre et à l'Est de l'Afrique ainsi qu'en Asie du Sud (Figure 2). Cette disparité de l'incidence à travers le monde peut être expliquée en partie par des expositions différentes aux facteurs de risques de cancer du sein incluant les facteurs héréditaires, génétiques et environnementaux, des différences de mode de vie et de comportements reproductifs des femmes, mais aussi par des différences liées aux activités de dépistage ainsi qu'aux méthodes diagnostiques du cancer du sein [15–17].



**Figure 1** : Taux d'incidence standardisés sur la population mondiale de cancer du sein dans le monde (pour 100 000 femmes).

Source : Global Cancer Observatory (GCO), Centre International de Recherche sur le Cancer (CIRC)-2018 [13].





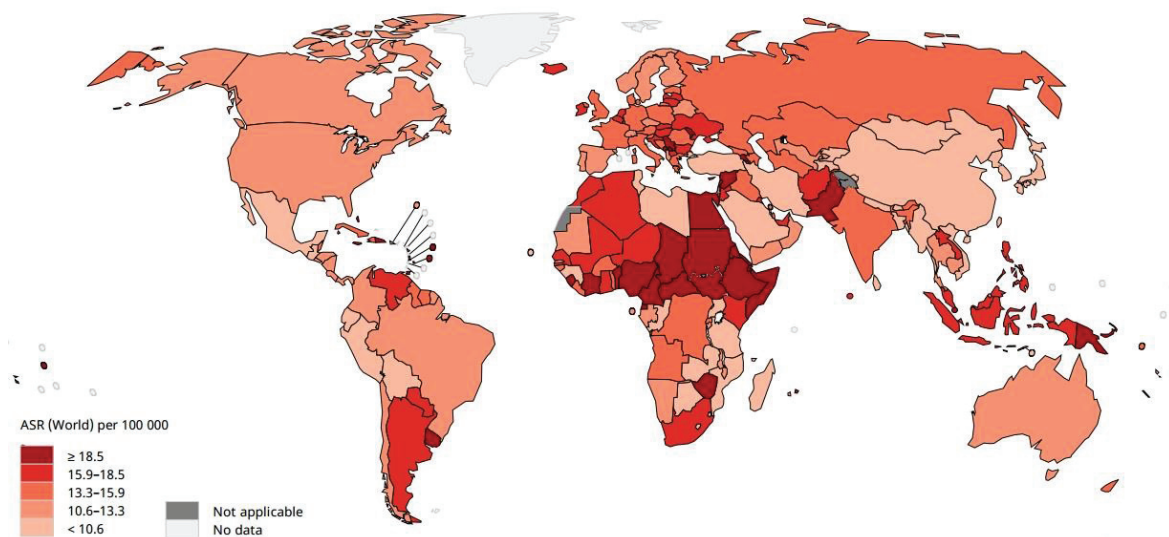
**Figure 2 :** Taux d'incidence standardisés sur la population mondiale de cancer du sein par région (pour 100 000 femmes).

Source : GCO, CIRC- 2018 [13].

### 2.1.1. Mortalité par cancer du sein

Le cancer du sein est la principale cause de décès par cancer chez la femme dans le monde. Avec un nombre de décès estimé à environ 626 679 en 2018, Il représente 15,0 % de l'ensemble de décès liés au cancer chez les femmes [13].

Les taux de mortalité standardisés sur l'âge du cancer du sein sont généralement en augmentation dans les pays en voie de développement, alors que qu'ils sont relativement en baisse ou stable dans la plupart des pays développés [18,19]. Cette disparité dans l'évolution de la mortalité liée à ce cancer peut être expliquée par le diagnostic plus précoce lié au dépistage généralisé dans la plupart des pays développés, et par l'amélioration de la prise en charge de cette maladie grâce à l'utilisation des schémas thérapeutiques plus efficaces [17,20,21]. Malheureusement, dans les pays en voie de développement le diagnostic du cancer du sein est fait généralement à des stades avancés [22].



**Figure 3 :** Taux de mortalité standardisés sur la population mondiale par cancer du sein dans le monde (pour 100 000 femmes).

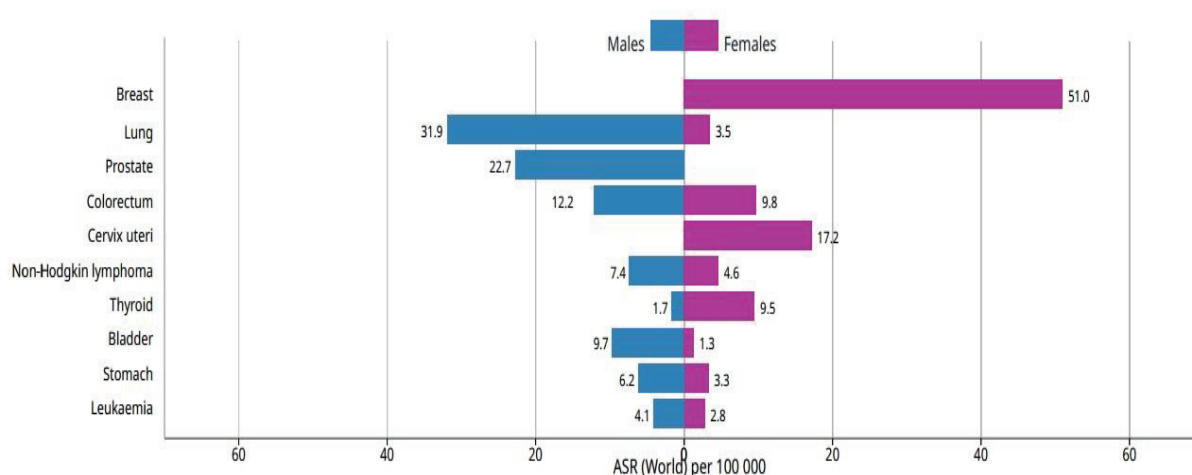
Source : GCO, CIRC- 2018 [13].

## 2.2. Au Maroc

### 2.2.1. Incidence du cancer du sein

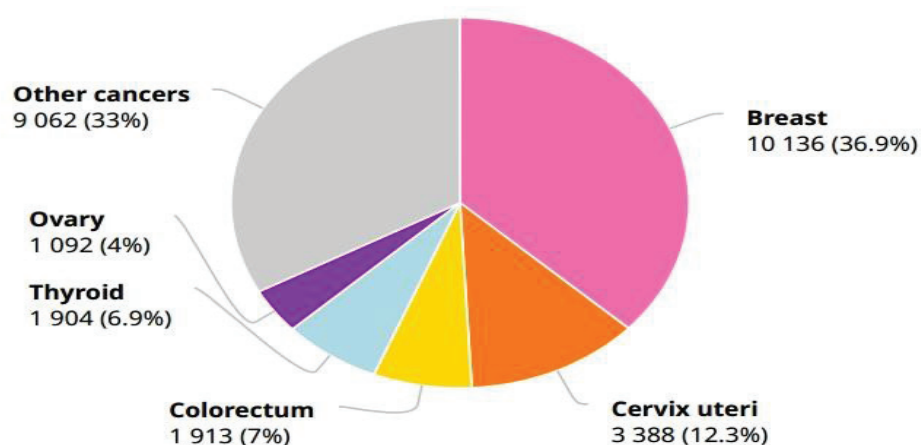
#### **Données de "Global Cancer Observatory", CIRC- 2018**

Avec environ 10 136 nouveaux cas estimés au Maroc en 2018, le cancer du sein représente le premier cancer chez la femme Marocaine. Le taux d'incidence standardisé sur la population mondiale est de 51 pour 100 000 femmes en 2018 (Figure 4). Il représente 36,9% de l'ensemble des cas de cancer diagnostiqués chez les femmes (Figure 5) et environ 19,2% de l'ensemble des cas diagnostiqués chez les deux sexes.



**Figure 4 :** Taux d'incidence standardisés sur la population mondiale pour des 10 premiers cancers au Maroc (pour 100 000 personnes).

Source: GCO, CIRC- 2018 [13].



**Figure 5 :** Estimation du nombre de nouveaux cas de cancer chez la femme au Maroc.  
Source: GCO, CIRC- 2018 [13].

### **Données nationales**

Le Maroc ne disposant pas d'un registre national pour mesurer l'incidence du cancer sur l'ensemble du territoire. De ce fait, l'incidence est estimée à partir de deux registres de population, considérés la principale source de données fiables en terme de morbidité du cancer au Maroc : le registre des cancers du Grand Casablanca [23] et le registre des cancers de Rabat [24], qui couvrent environ 12,0% et 2,1% de la population marocaine, respectivement.

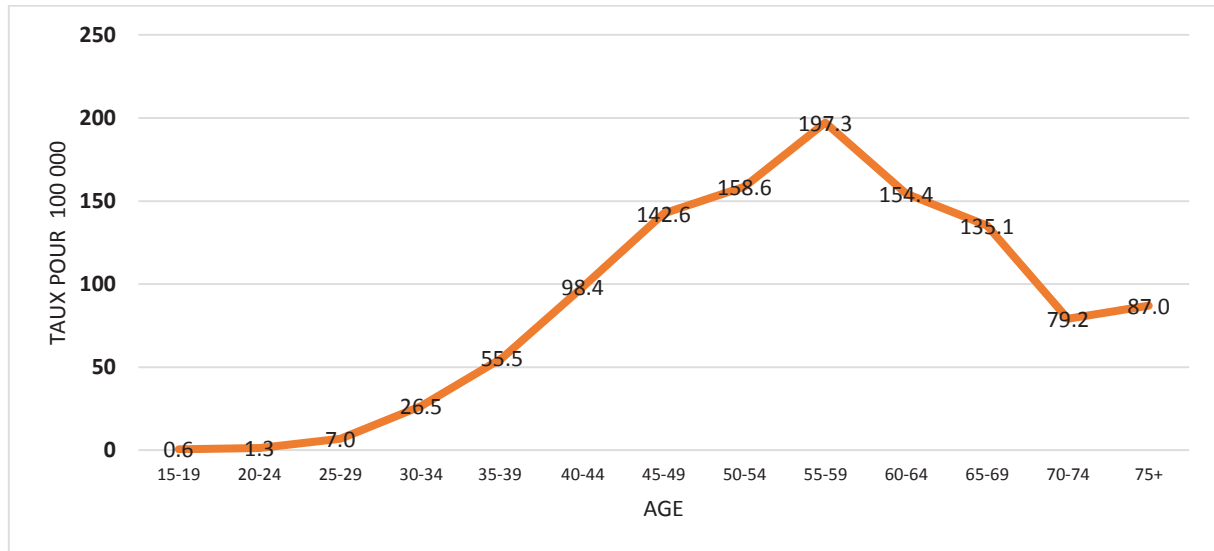
Entre 2008 et 2012, les données de registre de cancer du Grand Casablanca indiquent que le taux d'incidence du cancer du sein standardisé sur la population mondiale est de 49,5 pour 100 000 femmes. L'incidence du cancer du sein a considérablement augmenté entre 2008 et 2011, passant de 47,0 en 2008 à 52,2 en 2011, soit une augmentation annuelle de 3,68 %. L'incidence a légèrement diminué en 2012 (Tableau 1).

**Tableau 1.** Nombre de cas, incidence brute et standardisée sur la population mondiale du cancer du sein (pour 100 000 femmes), registre des cancers du Grand Casablanca 2008 – 2012.

	2008	2009	2010	2011	2012	2008-2012
Nouveaux cas	887	1062	902	1023	920	4794
Incidence brute	45,1	53,0	44,2	49,3	43,5	47,0
Incidence standardisée (population mondial)	47,0	54,7	47,1	52,2	46,6	49,5

Source : Registre des cancers du Grand Casablanca 2008 – 2012 [23].

L'incidence du cancer du sein varie en fonction de l'âge de la femme Marocaine. Les catégories d'âge ayant les taux d'incidence spécifique les plus élevées sont 55–59 ans, 50–54 ans et 60–64 ans avec 197,3, 158,6 et 154,4 pour 100 000, respectivement (Figure 6).



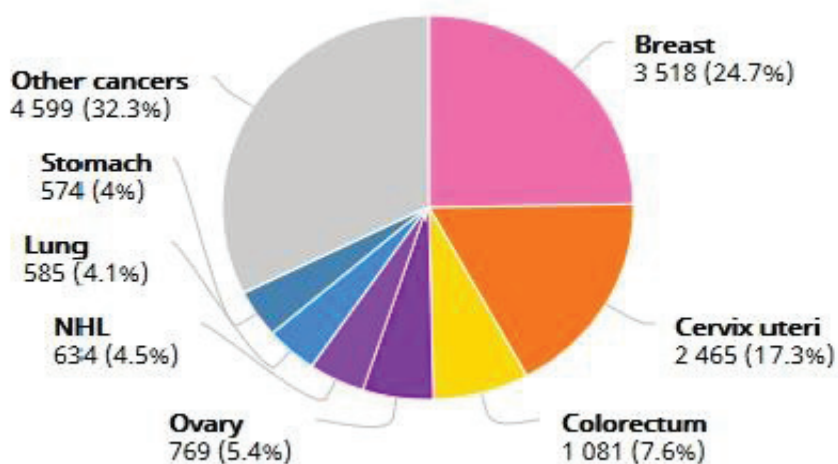
**Figure 6 :** Taux spécifiques selon l'âge de l'incidence du cancer du sein, registre des cancers du Grand Casablanca 2008 – 2012.

Source : Registre des cancers du Grand Casablanca 2008 – 2012 [23].

### 2.2.2. Mortalité par cancer du sein

En l'absence de données réelles sur la mortalité liée au cancer sein au Maroc, les estimations sont basées sur les données publiées par GCO, de CIRC [13].

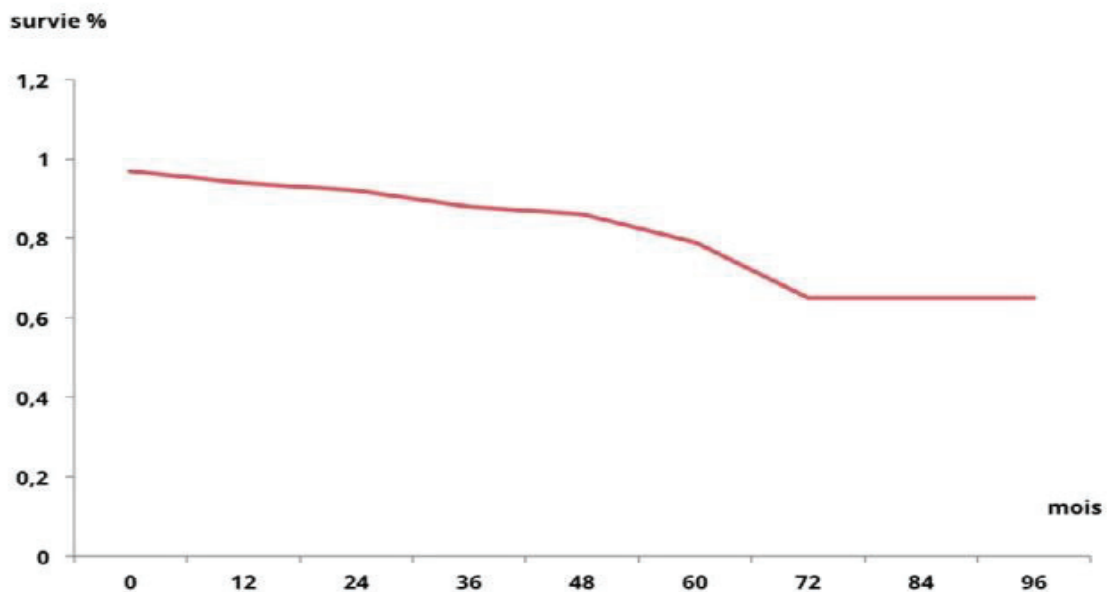
Selon GCO, le taux de mortalité standardisé sur la population mondiale par cancer du sein au Maroc est de 17,6 pour 100 000 femmes en 2018. Le cancer du sein est la première cause de mortalité par cancer chez la femme Marocaine. Il représente 24,7 % des décès liés aux cancers féminins, avec environ 3518 décès en 2018 (Figure 7).



**Figure 7** : Estimation du nombre des cas de décès par cancer chez la femme au Maroc.  
Source : GCO, CIRC- 2018 [13].

### 2.2.3. Survie du cancer du sein

Selon les données publiées dans le dernier rapport de registre des cancers du Grand Casablanca 2008 – 2012 [23], la survie globale à 5 ans et à 7 ans des cas de cancer du sein était de 79% et 65%, respectivement.



**Figure 8** : Courbe de survie des cas de cancer du sein diagnostiqués en 2008 au registre des cancers du Grand Casablanca.

Source : Registre des cancers du Grand Casablanca 2008 – 2012 [23].

## 3. Facteurs de risque de cancer du sein

Le cancer du sein est une maladie multifactorielle et complexe. Les facteurs de risque de cancer du sein chez la femme varient considérablement d'une population à l'autre. Plusieurs facteurs peuvent être impliqués dans la survenue du cancer du sein à savoir les facteurs hormonaux, reproductifs, génétiques ou héréditaires, environnementaux, et les facteurs liés au style de vie. Cependant, l'étiologie du cancer du sein demeure en partie inconnue.

### 3.1. Âge

Généralement, le risque de développer un cancer du sein augmente en fonction de l'âge mais n'est pas d'une manière linéaire [25,26]. Au Maroc, selon les données du registre des cancers du Grand Casablanca 2008 – 2012, l'incidence du cancer du sein chez les femmes Marocaines augmente linéairement avec l'âge avant 60 ans, puis diminue légèrement pour se stabiliser au-delà de l'âge 70 ans. Un pic a été observé chez la classe d'âge entre 55 et 59 ans (Figure 6).

### **3.2. Facteurs hormonaux et reproductifs**

#### ***Âge de la puberté et de la ménopause***

Une longue durée de la vie reproductive caractérisée par une puberté précoce et/ ou une ménopause tardive est associée à un risque élevé du cancer du sein [27,28]. Pour chaque année de retard de puberté (âge de la ménarche), le risque de la survenue d'un cancer du sein diminue par environ 5 %. Tandis que ce risque augmente d'environ 3 % pour chaque année supplémentaire d'âge à la ménopause [27].

#### ***Parité***

Un nombre élevé des grossesses menées à terme est associé à une diminution du risque de cancer du sein. Comparées avec les femmes nullipares, les femmes ayant au moins un enfant ont un risque réduit de cancer du sein d'environ 25 % [26]. Pour un âge égal à la première grossesse, cette diminution de risque est estimée à 7 % pour chaque nouvelle naissance [29]. Par ailleurs, il est important de noter que les grossesses menées à terme agissent sur le risque de cancer du sein d'une manière bi-phasique. Le risque est légèrement augmenté pendant les années qui suivent la grossesse, avec un pic de risque après 5 ou 10 ans, suivie d'une diminution de risque à plus long terme [26,30,31].

#### ***Âge à la première grossesse***

L'âge tardif à la première grossesse est associé à une augmentation de risque de cancer du sein, indépendamment de la parité. Les femmes ayant leur première grossesse à terme avant l'âge de 30 ans ont un risque de cancer du sein réduit de 25 % par rapport aux femmes nullipares [32]. Toutefois, le risque d'avoir un cancer du sein augmente d'environ 3 % pour chaque année supplémentaire à l'âge de la première grossesse [33]. Cette augmentation de risque est un peu plus élevée chez les femmes en préménopause [34].

#### ***Allaitement***

L'allaitement un facteur protecteur important pour le cancer sein, quelle que soit le statut ménopausique de la femme. L'allaitement pour une durée totale supérieur à 12 mois est associé à une diminution significative du risque de cancer du sein de 26% par rapport au fait de ne jamais allaiter [35]. En outre, la diminution de risque de cancer du sein est estimée à 4,5 % par année additionnelle d'allaitement, à nombre d'enfants égal [33].

#### ***Contraception orale***

L'utilisation de contraceptifs oraux, généralement combinant l'œstrogène et le progestatif, est associée à une augmentation de la survenue du cancer du sein. En effet, les femmes ayant utilisées une contraception orale ont un risque augmenté d'environ 24% par rapport aux femmes n'ayant jamais pris de contraceptifs [36]. Ce risque s'atténue progressivement après l'arrêt de l'utilisation et disparaît presque complètement après dix ans de l'arrêt définitif de l'utilisation de ces contraceptifs. Par ailleurs, il est rapporté que ni la durée d'utilisation de contraceptif oral, ni le type d'hormones (d'estrogène ou de progestatif) ne semblent faire varier le risque de cancer du sein [36,37].

### ***Traitement hormonal substitutif de la ménopause***

Les traitements hormonaux de la ménopause associant œstrogènes et progestatifs de synthèse sont fortement impliqués dans le risque du cancer du sein. Le risque augmente significativement avec la durée d'utilisation [38,39]. Les femmes qui utilisent les traitements hormonaux substitutifs de la ménopause pendant plus de cinq ans, ont un risque élevé de développer un cancer du sein de 26 à 35 %, comparées aux non utilisatrices [38]. Ce risque diminue progressivement après l'arrêt du traitement.

### **3.3. Antécédents familiaux et facteurs génétiques**

#### ***Antécédents familiaux***

L'existence d'antécédents de cancer du sein dans la famille constitue un facteur de risque majeur de cancer du sein. Ce risque augmente avec le nombre d'apparentés du premier degré (mère, sœur, fille) atteints de cancer du sein [40]. En effet, les femmes ayant dans leur famille un, deux ou trois parents du 1<sup>er</sup> degré atteints d'un cancer du sein, présentent respectivement un risque deux, trois et quatre fois plus élevée par rapport aux femmes sans antécédents [40].

#### ***Prédisposition génétique***

Certaines mutations génétiques sont associées à un risque accru de développer un cancer du sein. Globalement, les mutations génétiques plus impliqués sont la mutation du gène BRCA 1 situé sur le chromosome 17q21, et la mutation du gène BRCA 2 situé sur le chromosome 13q12 [41,42]. En effet, les femmes portant une mutation du gène BRCA 1 ont un risque cumulé de 65% de développer un cancer du sein [43]. Cette augmentation de risque est estimée à 45% chez les femmes porteuses d'une mutation du gène BRCA 2 [43]. D'autres mutations génétiques sont susceptibles d'augmenter le risque de développer un cancer du sein, à savoir les mutations des gènes ATM, CHEK2 et TP53 [44–46]. Généralement, les femmes avec une prédisposition génétique héritée représentent environ 5 à 10 % de l'ensemble des cas de cancers du sein [47,48].

### **3.4. Maladies bénignes du sein**

Les maladies bénignes du sein (ou mastopathies) constituent un facteur de risque de cancer du sein. Ce risque varie généralement en fonction de caractère prolifératif de la maladie [49,50]. On distingue trois catégories de maladies bénignes du sein : les lésions non prolifératives, les lésions prolifératives sans atypie et les lésions prolifératives avec atypie. Les lésions non prolifératives et prolifératives sans atypie sont associées à une faible augmentation de risque de cancer du sein, alors que les lésions prolifératives avec atypie augmentent ce risque d'au moins quatre fois par rapport à une absence de cette lésion [26,51].

### **3.5. Densité mammaire**

Une forte densité mammaire généralement caractérisée par une grande composante radio opaque (les tissus épithéliaux et conjonctifs) à la mammographie est un facteur de risque de cancer du sein. Les femmes ayant des seins très denses à la mammographie ont un risque élevé de la survenue d'un cancer du sein [52]. Ainsi, ce risque est multiplié de cinq fois chez

les femmes ayant une densité mammaire supérieure à 75 % comparées aux femmes ayant une densité mammaire de moins de 10 % [53].

### **3.6. Facteurs liés au mode de vie et nutrition**

Plusieurs facteurs liés au mode de vie sont reliés au risque de cancer du sein.

#### ***Activité physique***

Selon le dernier rapport de World Cancer Research Fund International (WCRF) & American Institute for Cancer Research (AICR) [54], l'activité physique vigoureuse est classée comme un facteur protecteur pour le cancer du sein en pré et en post-ménopause. Le risque est diminué d'environ 27 % chez les femmes exerçant une activité physique vigoureuse comparativement aux femmes qui n'exercent pas [55]. Généralement, l'effet protecteur de l'activité physique dépend de son intensité, une activité physique intense est considérée plus bénéfique dans la réduction de la survenue du cancer du sein qu'une activité de faible intensité [55–57].

#### ***Facteurs anthropométriques***

Globalement, l'association entre les facteurs anthropométriques et le risque de cancer du sein est complexe et elle diffère en fonction de statut ménopausique de la femme.

Le dernier rapport de World Cancer Research Fund International et American Institute for Cancer Research [54], a classé ces facteurs anthropométriques comme suit :

##### Cancer du sein avant la ménopause :

- ▷ Etre en surpoids ou obèses à l'âge de 18 à 30 ans diminue le risque de cancer du sein avant la ménopause.
- ▷ Etre en surpoids ou obèse à l'âge adulte avant la ménopause diminue le risque de cancer du sein chez les femmes pré-ménopausiques.
- ▷ Les facteurs de développement conduisant à une plus grande croissance linéaire (marquée par la taille atteinte chez l'adulte) augmentent le risque de cancer du sein.
- ▷ Les facteurs qui entraînent une augmentation du poids à la naissance, ou ses conséquences, augmentent le risque de cancer du sein en préménopause.

##### Cancer du sein après la ménopause :

- ▷ Etre en surpoids ou obèses à l'âge de 18 à 30 ans est associé à une réduction de risque de cancer du sein après la ménopause.
- ▷ Etre en surpoids ou obèse à l'âge adulte augmente le risque de cancer du sein en post-ménopause.
- ▷ Le gain de poids important à l'âge adulte augmente le risque de cancer du sein chez les femmes en post-ménopause.
- ▷ Les facteurs de développement conduisant à une plus grande croissance linéaire (marquée par la taille atteinte chez l'adulte) augmentent le risque de cancer du sein après la ménopause.



### ***Tabagisme***

Le tabagisme actif est classé par le CIRC comme étant un facteur de risque probable (agents cancérigène avec indications limitées) pour le cancer du sein [58]. Certaines données de la littérature supportent l'association positive entre le tabagisme actif et le cancer du sein et soulignent le rôle important de la durée et l'âge à l'exposition dans cette association [59–61]. Il est également suggéré que le tabagisme passif peut entraîner une légère augmentation de risque de cancer du sein [61,62].

### ***Alimentation (incluant l'alcool)***

La consommation d'alcool est reconnue comme un facteur de risque de cancer du sein en pré comme en post-ménopause [54]. Pour une consommation d'un verre d'alcool par jour (environ 10g d'éthanol) le risque de cancer du sein augmente de 7 à 12 % [63,64].

Dans leur dernier rapport, le World Cancer Research Fund International et American Institute for Cancer Research, suggèrent une probable association (preuves limitées) entre un régime alimentaire riche en calcium et la diminution du risque de cancer du sein, ainsi que la consommation des produits laitiers peuvent diminuer ce risque chez les femmes en préménopause [54].

Certaines études épidémiologiques examinant la relation entre les profils alimentaires et cancer du sein suggèrent que les profils alimentaires sains « définis à posteriori », particulièrement riches en fruits, légumes et céréales complètes et pauvres en gras saturés, viandes rouges et charcuteries, réduit le risque de cancer du sein d'environ 10% [65–68]. D'autres données de la littérature, montrent que l'adhésion à certains régimes alimentaires, basés sur des scores pré-établis « définis à priori » (exemple : score d'alimentation méditerranéenne), est associée à un risque réduit de cancer du sein [69].

## **3.7. Facteurs environnementaux et professionnels**

### ***Exposition aux radiations ionisantes***

Le Centre International de Recherche sur le Cancer a classé les rayons X et gamma comme étant des cancérigènes reconnus avec preuves suffisantes pour le cancer du sein féminin [58]. L'exposition du tissu mammaire aux radiations ionisantes est associée d'une manière linéaire au risque de cancer du sein [70–72]. Ce risque dépend beaucoup de l'âge à l'exposition, les femmes exposées à une radiation de 1 Gy avant l'âge de 40 ans ont trois fois plus de risque d'avoir un cancer du sein [73]. Par ailleurs, les résultats concernant l'exposition aux radiations non-ionisantes (champs électromagnétiques) sont plus controversés [70,74,75].

### ***Travail de nuit et travail posté***

Travail de nuit et travail posté sont susceptibles de provoquer un cancer du sein chez les femmes. Le travail posté impliquant une perturbation du rythme circadien est classé par le Centre International de Recherche sur le Cancer comme un facteur de risque probable (Group 2A) de cancer du sein [58]. Le travail de nuit pour une longue durée pourrait augmenter le risque de cancer du sein d'environ 31 % chez les femmes [76].

#### 4. Anatomie et physiologie de la glande mammaire

La glande mammaire est une glande exocrine, tubulo-alvéolaire, dont la fonction est la sécrétion lactée. Elle présente 15 à 20 glandulaires indépendantes (lobes) qui sont séparées par du tissu graisseux et des bandes de tissu conjonctif dense appelées ligaments de Cooper. Chaque lobe est subdivisé en lobules et alvéoles (élément synthétiseur et sécréteur de lait). Des canaux drainent séparément chacun des lobes et débouchent à la surface du mamelon par des pores indépendants [77,78].

Le développement de la glande mammaire débute au cours de la période embryonnaire. Sa prolifération et sa différenciation se font au moment de la puberté sous contrôle de deux hormones : les estrogènes, qui stimulent la croissance et les ramifications du système canalaire ainsi que la prolifération du tissu adipeux, et la progestérone dont l'action combinée à celle des estrogènes aboutit à la différenciation des structures lobulaires.

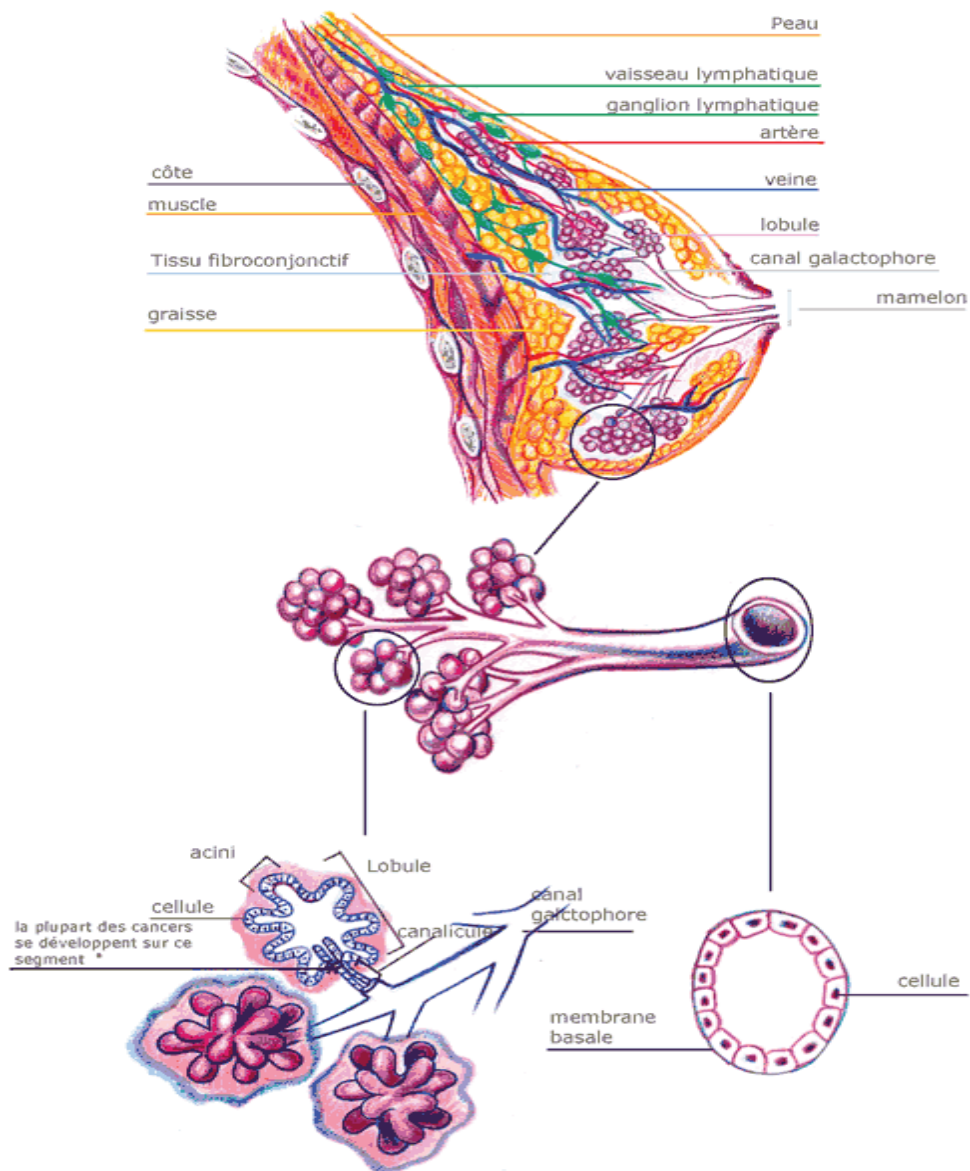


Figure 9 : Anatomie du sein.

Source : <http://centre-des-coteaux.be/>

## 5. Justification et objectifs de la thèse

Au Maroc, le cancer du sein constitue un véritable problème de santé publique du fait de sa charge de morbidité et de mortalité lourde et de son impact socioéconomique. Son incidence a connu une augmentation rapide durant les dernières années. Cette augmentation peut être attribuée pour une grande part aux modifications du mode de vie (obésité, habitudes alimentaires, manque de l'activité physique, etc.), du comportement reproductif des femmes (parité, allaitement, etc.), et de l'environnement à l'origine d'une transition épidémiologique pouvant entraîner une plus grande fréquence d'exposition à certains facteurs de risque de cancer du sein.

En Afrique du nord peu d'études ont été menées sur les facteurs de risque associés au cancer du sein, tandis que les femmes de cette région ont des caractéristiques différentes de celles des pays occidentaux, notamment en ce qui concerne le nombre d'enfants, l'âge à la première grossesse, la durée de l'allaitement maternel, l'utilisation des thérapies hormonales substitutives et la consommation d'alcool. Actuellement au Maroc, les études réalisées sur ce sujet restent très rares et généralement non publiées. Dans la région de Fès, dont la population dépasse deux millions d'habitants, aucune étude sur les facteurs de risque de cancer du sein chez la femme n'avait jusqu'alors été publiée.

Ces questions de recherche nous ont amené à développer et mettre en place deux études cas-témoins sur les facteurs de risque de cancer du sein dans la région de Fès : "Fez Breast Cancer Study" réalisée en 2014 – 2015, et "BreCaFez Study" réalisée en 2016 – 2017.

**Ce projet de thèse a pour objectif général** de déterminer les principaux facteurs de risque reconnus et suspectés de cancer du sein (hormonaux, reproductifs, anthropométriques, professionnels, et de style de vie) chez les femmes marocaines dans la région de Fès, Maroc.

Plus spécifiquement, ce projet de thèse a pour objectifs :

1. De faire le point des connaissances sur l'évolution de l'incidence et de la mortalité liée au cancer du sein au Maroc. Ce travail s'appuiera sur les données de la littérature.
2. De réaliser une analyse complémentaire et publication des résultats de l'étude "Fez Breast Cancer Study" mis en place en 2014. Principalement, évaluer l'association entre les facteurs reproductifs et menstruels et le risque de cancer du sein dans la région de Fès en se basant sur les données déjà collectées dans le cadre de "Fez Breast Cancer Study".
3. De mettre en place une nouvelle étude cas-témoins "BreCaFez Study" dans la région de Fès, permettant de satisfaire aux standards internationaux de qualité épidémiologique qui inclut cette fois, en plus des facteurs de risque reproductifs classiques, les détails sur le style de vie, les mesures anthropométriques, les habitudes alimentaires, l'exposition professionnelle et l'exposition aux produits phytosanitaires.
4. D'explorer les associations entre les mesures anthropométriques, le style de vie, les professions et le risque de cancer du sein, on se basant sur les données de "BreCaFez Study".
5. De préparer et valider les outils nécessaires pour l'analyse des données nutritionnelles et risque de cancer du sein, adaptés au contexte marocain.

**6.** De participer au développement et à la mise en place d'une étude multicentrique sur le cancer du sein au Maroc : "EDSMAR Study" coordonnée par le CIRC, qui inclut une récolte d'informations cliniques et histologiques, et des échantillons biologiques (sang, urines et tissus tumoraux) selon des protocoles internationaux strictement contrôlés.

## Chapitre II : Présentation des études

### 1. Fez Breast Cancer Study

#### 1.1. Design de l'étude

Fez Breast Cancer Study est une étude cas-témoins avec appariement sur l'âge ( $\pm 3$  ans), réalisée au Centre Hospitalier Universitaire (CHU) Hassan II de Fès entre janvier 2014 et avril 2015. Son objectif principal était d'explorer l'association entre les facteurs reproductifs et menstruels et le risque de cancer du sein chez les femmes de la région de Fès.

Le protocole de cette étude a été approuvé par le comité d'éthique de Centre hospitalier Hassan II de Fès.

Au total, 237 cas et 237 témoins ont été recrutés dans cette étude.

#### 1.2. Sélection des cas

Il s'agit des patientes admises pour un cancer du sein (in situ ou invasif) confirmé par un examen histologique, au centre d'oncologie de CHU de Fès qui reçoit des cas de cancer du sein de différents types et stades.

#### 1.3. Sélection des témoins

Il s'agit des accompagnatrices des patients admis au Centre des Consultations Externes du CHU de Fès, qui reçoit des consultants de différentes spécialités chirurgicales et médicales venant de toute la région de Fès. Les accompagnatrices des patientes suivies pour un cancer du sein ont été exclues de cette étude.

Nous avons eu des difficultés à trouver des accompagnatrices dont l'âge est supérieur ou égal à 60 ans. Des accompagnatrices choisies au hasard nous ont indiqué les coordonnées d'autres femmes remplissant cette exigence d'âge. Ces dernières ont été appelées par téléphone, pour solliciter leur accord de participation à l'étude, et fixer la date et le lieu de l'entretien en face à face.

#### 1.4. Recueil des données

Le recueil des données de cette étude a été réalisé par six enquêteurs formés à cet effet, les questionnaires ont été administrés en face à face de manière standardisée aux cas et aux témoins.

Nous avons collecté des informations sur :

- Les caractéristiques sociodémographiques : âge, statut matrimonial, niveau de scolarité, statut d'emploi, revenu mensuel du ménage, etc.
- Les mesures anthropométriques : poids, taille, etc.
- Les antécédents familiaux de cancer : degré de parenté, localisation du cancer, etc.
- Le tabagisme : statut tabagique au moment de l'entretien, âge au début/ arrêt de la consommation, quantité de cigarettes consommées par jour, exposition passive au tabac, etc.
- L'alcool : histoire de la consommation d'alcool.
- Les facteurs hormonaux et reproductifs : âge aux premières règles, longueur du cycle menstruel, statut ménopausique, âge de la ménopause, nombre d'enfants, nombre de

grossesses menées à terme, fausses couches, avortements provoqués, âge à la première grossesse, allaitement maternel, histoire d'une éventuelle stérilité, prise de contraceptifs oraux et de traitements hormonaux de la ménopause, etc.

- L'activité physique : les données sur l'activité physique ont été recueillies en utilisant le questionnaire mondial sur la pratique d'exercice physique Global Physical Activity Questionnaire 2 (GPAQ version 2) [79], qui permet de recueillir des informations sur la pratique d'exercice physique dans les trois situations (activités au travail, se déplacer d'un endroit à l'autre, activités de loisirs), ainsi que sur les comportements sédentaires.

### **1.5. Puissance de l'étude**

Le logiciel Epi Info 7 a été utilisé pour estimer la puissance de cette étude. En effet, elle peut par exemple détecter un odds ratio (OR) de 1,9 avec une fréquence de l'exposition chez les témoins de 15%, une erreur de 1<sup>ère</sup> espèce (risque  $\alpha$ ) de 5%, et une puissance de 80% (risque  $\beta$  = 20%).

#### Financement

Cette étude n'a bénéficié d'aucun soutien financier.

## **2. BreCaFez Study**

### **2.1. Design de l'étude**

BreCaFez Study est une étude cas-témoins avec appariement sur l'âge ( $\pm$  5 ans) et sur le milieu de résidence, réalisée dans la région de Fès entre Février 2016 et Août 2017. Son objectif était de déterminer les principaux facteurs de risque du cancer du sein chez les femmes de la région de Fès, Maroc.

Le protocole de l'étude a été approuvé par le comité d'éthique de la Faculté de Médecine et Pharmacie de Casablanca et par la Commission nationale de contrôle de la protection des données à caractère personnel (Autorisation n° A-RS-192-2015).

Au total, 300 cas et 300 témoins ont été recrutés dans cette étude.

### **2.2. Sélection des cas et des témoins**

Le recrutement des cas a été effectué au centre d'oncologie de CHU de Fès. Les cas sont (1) des cas incidents de cancer du sein primaire (in situ ou invasif) confirmés histologiquement; (2) avant le début de tout traitement de la tumeur (chimiothérapie, radiothérapie, hormonothérapie ou chirurgie) ; et (3) en mesure de participer et de fournir un consentement éclairé signé pour la participation à l'étude.

Les témoins ont été choisies aléatoirement parmi les femmes visitant l'un de six centres de santé de base (3 en secteur urbain et 3 en secteur rural) situés dans la région de Fès. Les femmes ayant des antécédents de cancer ont été exclues de cette étude.

Les femmes enceintes, allaitantes, ou suivies pour une insuffisance rénale chronique (cas ou témoins) ont été exclues de cette étude.

### 2.3. Recueil des données

Des entretiens en face-à-face ont été effectués par du personnel de santé qualifié (4 enquêtrices) formé à cet effet, en utilisant des questionnaires standardisées et adaptés à la population marocaine (dialecte arabe marocain).

#### Questionnaire général :

Le questionnaire général est très détaillé et se compose de 16 sections :

1- Informations générales : âge, adresse, résidence, détails sur la naissance, statut matrimonial, niveau d'étude, etc.

2- Statut socioéconomique : nous avons utilisés un questionnaire validé au niveau régional pour calculer l'index socioéconomique des femmes de notre étude [80].

3- Activités de travail / professions : les informations détaillées ont été collectées pour chaque emploi occupé pour une durée supérieure à 6 mois au cours de la carrière : poste de travail occupé, date début / fin, activité ou production de l'entreprise, nombre d'heures de travail, tâches effectuées, histoire de travail posté et de travail de la nuit, etc.

4- Exposition aux produits phytosanitaires : exposition domestique et professionnelle, fréquence d'utilisation, etc.

5- Consanguinité des parents : type et degré de consanguinité.

6- Facteurs anthropométriques : poids, taille debout, taille assise, tour de taille, tour de hanches, poids à différents âges, etc.

L'échelle validée de Sørensen [81] a été utilisée pour la collection des données sur la silhouette des femmes à différents âges.

7- Tabagisme : statut tabagique actuel, histoire détaillée sur la consommation du tabac, exposition passive au tabac, etc.

8- Alcool : histoire détaillée sur de la consommation d'alcool, type, fréquence, quantité, etc.

9- Antécédents médicaux personnels : les antécédents et le cas échéant l'âge au début de la maladie ont été recueillis. Des questions spécifiques à certaines maladies ont été également posées : diabète, obésité, hypertension artérielle, tumeurs malignes, acné, etc.

10- Utilisation des médicaments : l'histoire sur l'utilisation de certains médicaments : anti-inflammatoires non-stéroïdiens, antidépresseur, etc.

11- Histoire du cancer dans la famille : degré de parenté, localisation du cancer, âge au diagnostic, etc.

12- Facteurs hormonaux et reproductifs : âge aux premières règles, cycle menstruel, statut ménopausique, âge de la ménopause, nombre d'enfants, nombre de grossesses menées à terme, fausses couches, avortements provoqués, âge à la première grossesse, âge à la naissance de chaque enfant, allaitement maternel, histoire d'une éventuelle stérilité, utilisation des contraceptifs oraux et des traitements hormonaux de la ménopause, etc.

13- Activité physique : les informations ont été recueillies sur la fréquence et le nombre d'heures passé par les femmes dans différents types d'activité physique (légère, modérée, de forte intensité) lors d'une semaine typique qui reflète l'activité physique pendant le 12 derniers mois. L'histoire sur l'activité physique et la pratique des exercices physiques vigoureux aux différents âges ont été également collectées.

14- Sommeil nocturne : heures habituelles, nombre d'heures, histoire d'insomnie, etc.

15- Exposition aux radiations : analyses radiologiques réalisées au cours de la vie, etc.

16- Autres expositions : utilisation de déodorant, anti-transpirant et colorants pour les cheveux, etc.

#### Questionnaire de fréquence alimentaire - Food Frequency Questionnaire (FFQ)

Le recueil des données sur les habitudes alimentaires durant les 12 mois précédant l'entretien, a été effectué à l'aide d'un Food Frequency Questionnaire (FFQ), adapté et validé au contexte marocain [82]. Ce FFQ inclus 255 items pour 32 groupes d'aliments consommés au Maroc.

#### **2.4. Puissance de l'étude**

Le logiciel Epi Info 7 a été utilisé pour estimer la puissance de cette étude. En effet, elle peut par exemple détecter un odds ratio de 1,9 avec une fréquence de l'exposition chez les témoins de 12%, une erreur de 1<sup>ère</sup> espèce (risque  $\alpha$ ) de 5%, et une puissance de 80% (Risque  $\beta$  = 20%).

#### Financement

Cette étude a été financée par Moffitt Cancer Center (The NIH International Fogarty Center for the award number 5D43TW009804, PI Anna Giuliano).



## Chapitre III : Résultats

### 1. Incidence et mortalité du cancer du sein chez les femmes au Maroc : Comparaison avec d'autres pays

#### 1.1. Introduction

Comme déjà évoqué dans la partie 2. 1. (Chapitre I : Introduction), au niveau mondial, le cancer le plus fréquent et le plus meurtrier chez la femme est le cancer du sein. Les taux d'incidence et de mortalité par ce cancer varient considérablement d'une région du monde à l'autre et plusieurs facteurs sont impliqués dans ces variations géographiques.

Par ailleurs, les données descriptives concernant les tendances de l'incidence et de la mortalité par cancer du sein sont d'une grande importance pour la recherche scientifique sur ce cancer, ainsi que pour la planification et l'évaluation des programmes de prévention et de contrôle de cette maladie.

Au Maroc, les données sur le cancer sein sont fournies uniquement par deux registres des cancers, il s'agit de registre des cancers du Grand Casablanca [23] et le registre des cancers de Rabat [24]. En revanche, des taux de la mortalité par ce cancer proviennent des estimations de GCO publiées par le CIRC [13].

Les études descriptives concernant l'incidence et la mortalité par cancer du sein chez les femmes Marocaines sont très rares. L'objectif de ce travail était de décrire les taux d'incidence et de mortalité par cancer du sein féminin au Maroc, en se basant sur les données les plus récentes (au moment la publication de cet article), et de les comparer avec celles observées dans la région et dans certains pays développés.

#### 1.2. Méthodes

Le taux d'incidence de cancer du sein chez la femme au Maroc a été analysé à partir des données des derniers rapports publiés par le registre des cancers du Grand Casablanca et le registre des cancers de Rabat pour la période 2004–2008.

Les taux d'incidence de cancer du sein dans les autres pays ont été collectés à partir des registres de cancer concernant ces pays et/ ou de données publiées par Forman et al., dans the Cancer Incidence in Five Continents, Volume X [83].

Pour les taux de mortalité par cancer du sein nous avons utilisé les données de GLOBOCAN 2012- CIRC [84].

#### 1.3. Principaux résultats

La tendance évolutive de l'incidence de cancer du sein chez la femme Marocaine, durant la période 2004–2008, montre une augmentation annuelle moyenne de 2,85 %. En effet, le taux d'incidence du cancer du sein standardisé sur la population mondiale est passé de 35,0 en 2004 à 39,0 en 2008. Ces taux d'incidence restent relativement bas comparativement à ceux qui étaient observées dans certains pays occidentaux, mais légèrement élevé comparativement à certains pays de la région comme la Tunisie et la Libye. Par ailleurs, les

taux d'incidence les plus élevés chez les femmes Marocaines étaient enregistrés dans les catégories d'âge 45–49 ans, 50–54 ans, et 55–59 ans avec 106,1, 108,2 et 108,5 pour 100 000 femmes, respectivement.

Avec un nombre de décès de 2 878 en 2012, le taux de mortalité standardisé sur la population mondiale du cancer du sein au Maroc était estimé à 18,0 pour 100 000 femmes en 2012. Ce taux était relativement similaire à celui observé dans certains pays de la région comme l'Algérie, mais un peu plus élevé par rapport au taux moyen de mortalité lié à ce cancer pour la population mondiale pendant la même année.

#### **1.4. Forces et faiblesses de l'étude**

Certaines limites de cette étude doivent être signalées. Premièrement, les données sur l'incidence de cancer du sein au Maroc sont basées sur les données fournies par le registre des cancers du Grand Casablanca et le registre des cancers de Rabat qui ne couvrent qu'environ 14,1 % de la population marocaine. Deuxièmement, les données sur la mortalité par cancer du sein sont basées sur des estimations de GLOBOCAN 2012 et pas sur des données collectées auprès de la population Marocaine. De plus, il n'existait pas d'information sur l'évolution de la mortalité au moment de la publication de cet article. Concernant les points forts de cette étude, il est important de signaler que les données d'incidence présentées dans cet article correspondaient à une période antérieure à la mise en œuvre d'un programme de dépistage précoce du cancer de sein datant de 2010. Ainsi, l'évolution d'incidence observée dans cette étude n'était pas influencée par les activités de ce programme.

#### **1.5. Conclusion**

Bien que les taux incidence du cancer du sein au Maroc restent relativement inférieurs à ceux observés dans certains pays occidentaux, ces taux sont en augmentation considérable au cours des dernières années. D'autre part, des efforts sont nécessaires pour établir des bases de données Marocaines pour le recueil d'informations plus fiables sur la mortalité par cancer du sein. Les études sur la survie du cancer du sein, qui sont très rares au Maroc, constituent des perspectives d'intérêt. Enfin, des stratégies efficaces de prévention et de contrôle du cancer du sein sont nécessaires dans notre pays.

## 1.6. Article 1

### **Female Breast Cancer Incidence and Mortality in Morocco: Comparison with Other Countries.**

Mohamed Khalis<sup>1,2,3</sup>, Karima El Rhazi<sup>1,3</sup>, Hafida Charaka<sup>1,3</sup>, Véronique Chajès<sup>4</sup>, Sabina Rinaldi<sup>4</sup>, Chakib Nejjari<sup>1,5</sup>, Isabelle Romieu<sup>4</sup>, Barbara Charbotel<sup>2</sup>

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*Breast Cancer Incidence and Mortality in Morocco*

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## RESEARCH ARTICLE

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### **Female Breast Cancer Incidence and Mortality in Morocco: Comparison with Other Countries**

**Mohamed Khalis<sup>1,2,3\*</sup>, Karima El Rhazi<sup>1,3</sup>, Hafida Charaka<sup>1,3</sup>, Véronique Chajès<sup>4</sup>, Sabina Rinaldi<sup>4</sup>, Chakib Nejjari<sup>1,5</sup>, Isabelle Romieu<sup>4</sup>, Barbara Charbotel<sup>2</sup>**

#### **Abstract**

**Background:** Breast cancer is the most frequently diagnosed malignancy and the leading cause of cancer death among women worldwide. In Morocco, there have been few recent descriptive studies on female breast cancer. The aim of this study was to describe the latest available incidence and mortality rates of breast cancer among Moroccan

## **Abstract**

**Background:** Breast cancer is the most frequently diagnosed malignancy and the leading cause of cancer death among women worldwide. In Morocco, there have been few recent descriptive studies on female breast cancer. The aim of this study was to describe the latest available incidence and mortality rates of breast cancer among Moroccan women and to compare them with rates in other regional and Western countries.

**Methods:** For this descriptive study, Moroccan incidence data were obtained from the most recent reports of the cancer registries of Casablanca and Rabat. Information on breast cancer incidence for different countries were obtained primarily from publicly available cancer registries and Cancer Incidence in Five Continents, Volume X. Mortality data were extracted from the GLOBOCAN 2012 published by the International Agency for Research on Cancer.

**Results:** The age-standardized incidence (World) rate of breast cancer in Moroccan women increased from 35.0 to 39.0 per 100,000 women between 2004 and 2008, showing an annual increase of 2.85 %. The highest incidence rates were registered in the age groups of 45-49, 50-54 and 55-59 years (106.1, 108.2 and 108.5 respectively). Sixty-nine percent of female breast cancer cases were diagnosed at stages II and III. In 2012, the estimated number of women who died of breast cancer in Morocco was 2,878. The crude, age-standardized (World) mortality rates were 17.3 and 18.0 per 100,000, respectively.

**Conclusion:** Although the incidence of female breast cancer in Morocco is lower than in Western countries, evidence shows that the rate is rising. This increase of breast cancer incidence has been observed in parallel with changes in reproductive behavior and adoption of a Western lifestyle. Prevention policies need to be implemented.

**Key words:** Breast cancer; Incidence; Mortality; Morocco.

## **Introduction**

Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death among women worldwide, with an estimated 1.7 million cases and 521 900 deaths in 2012. Breast cancer alone accounts for 25% of all cancer cases and 15% of all cancer deaths among females (Torre et al., 2015). Less developed countries account for about 55.6% of all breast cancer cases and 62.1% of deaths (Ferlay et al., 2013). Breast cancer incidence rates vary considerably across geographic regions (Ghoncheh et al., 2016). Overall, the rates are high in Northern America, Australia, New Zealand, and Northern and Western Europe; and lowest in most of Africa and Asia (Torre et al., 2015).

Although, the incidence of breast cancer in the North Africa region is lower than that in Western countries (approximately 1.5–2 times lower among females aged less than 50, and 3–4 times lower among females aged more than 50), the breast cancer picture in Northern Africa is changing (Corbex et al., 2014).

Morocco is a country with a population estimated at 33.8 million people in 2014, and a life expectancy at birth of 74.8 years in 2010 (High Commission for Planning, Morocco, 2016). According to the United Nations human development index (HDI), Morocco's HDI value for 2014 was 0.62, which places the country in the medium human development category (The United Nations Development program, 2015).

Morocco is a country in epidemiological transition, marked by a double burden due to the coexistence of infection and chronic diseases (Nejmi and Boutayeb, 2016), and the breast cancer is increasingly becoming an important public health concern (Slaoui et al., 2014). The incidence rate of this disease has risen in the past years, likely due to changes in the pattern of breast cancer risk factors caused by adoption of a Western lifestyle.

It is noteworthy that there are few recent descriptive studies on the incidence and mortality of breast cancer among Moroccan women. The aim of this study was to describe the latest available incidence and mortality rates of breast cancer among Moroccan women and to compare them to the rates of regional and Western countries.

## **Methods**

This descriptive study was carried out based on existing incidence and mortality data.

### *Moroccan incidence data*

In Morocco, two population-based registries are the principal sources of reliable cancer morbidity data: The first one, the population-based cancer registry of Casablanca, covering around 12 % of the Moroccan population. It provides incidence of all types of cancer from 2004 onwards among the population of the Greater Casablanca. The second one, the population-based cancer registry of Rabat, covering around 2.1 % of the Moroccan population, it reports all new cancer cases from 2005 onwards among residents in Rabat.

We obtained breast cancer incidence data from the most recent reports of these two cancer registries, corresponding to the periods: 2004 (Cancer Registry of Casablanca, 2004), 2005–2007 (Cancer Registry of Casablanca, 2005-2007) for the cancer registry of Casablanca and 2005 (Cancer Registry of Rabat, 2005), 2006–2008 (Cancer Registry of Rabat, 2006-2008) for the cancer registry of Rabat.

### *International incidence data*

Information on breast cancer incidence for different countries was obtained primarily from publicly available cancer registries and the Cancer Incidence in Five Continents, Volume X (Forman et al., 2014).

### *Mortality data*

In Morocco, there are no official published data about breast cancer mortality. In this study, breast cancer mortality estimates for the year 2012, were extracted from the GLOBOCAN 2012 published by the International Agency for Research on Cancer (IARC) (Ferlay et al., 2013).

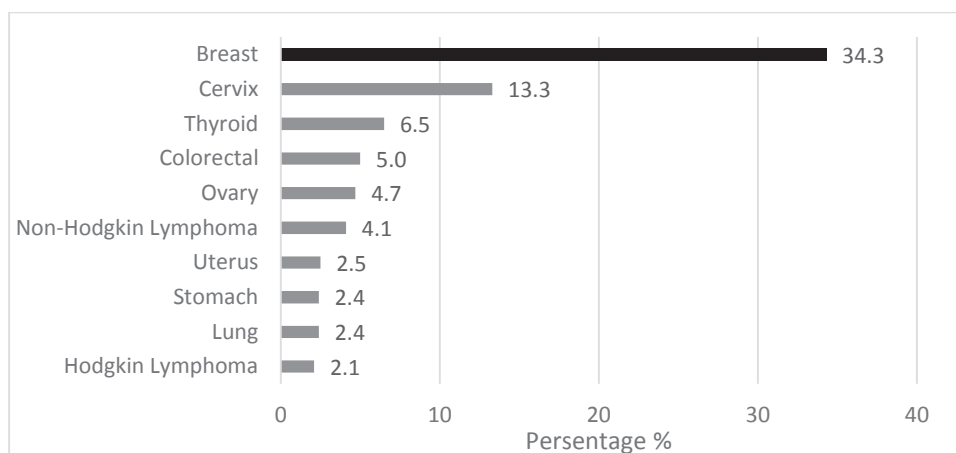
## Results

Breast cancer was the first leading cancer incidence in Moroccan women, accounting for 34.4% of all new cancer cases in females (Fig. 1, Fig. 2). Overall, the age-standardized incidence (World) rate of breast cancer increased from 35.0 to 39.0 per 100 000 women between 2004 and 2008, showing an annual increase of 2.85 % (Table 1). The age-standardized incidence (World) of breast cancer in Morocco was higher than that in neighboring countries (Fig. 3)

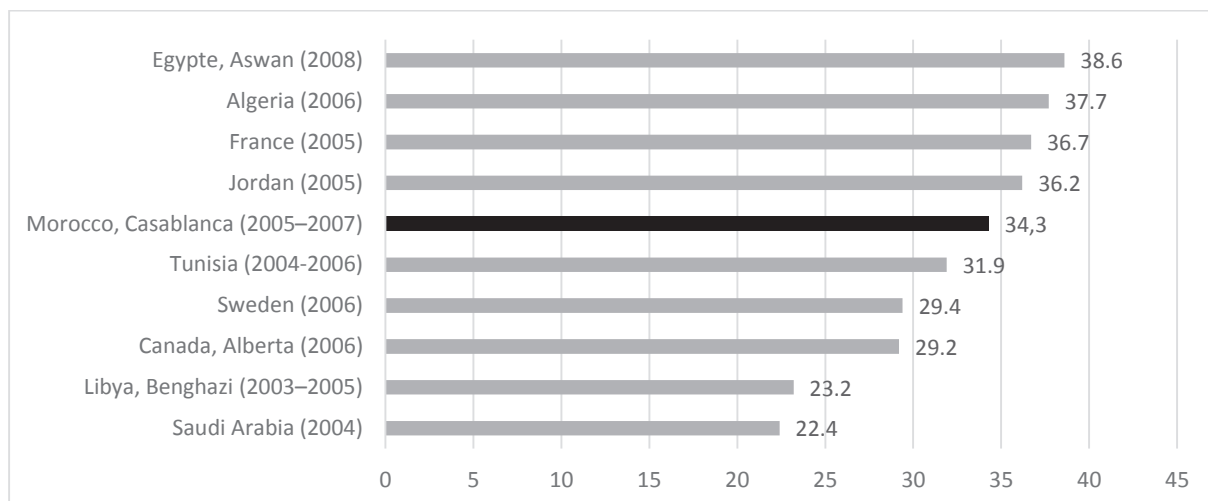
Between 2005 and 2007, the highest incidence rates were registered in the age groups of 45–49, 50–54 and 55–59 years (106.1, 108.2 and 108.5 respectively). Thereafter, the incidence rates decline to 86.5, 85.9, and 53.2 for the age groups of 65–69, 70–74 and 75+ years respectively (Table 2, Fig. 4).

For distribution of female breast cancer by stage and according to the Rabat cancer registry (2006-2008), 13.5% of female breast cancer were diagnosed at stages I, 44.6% at stages II, 24.4% at stages III and 4.5% at stages IV (13.0% not defined).

In 2012, the estimated number of women who died of breast cancer in Morocco was 2878. The crude, age-standardized (World) mortalities were 17.3 and 18.0 per 100 000, respectively (Table 3).



**Fig. 1.** Ten most common cancers among Moroccan women, according to the cancer registry of Casablanca 2005-2007.



**Fig. 2.** Breast cancer as proportion of all reported cancers in females in Morocco compared to other countries.

Data from: (Cancer Registry of Saudi Arabia, 2004; El Mistiri et al., 2015; Cancer Registry of Canada- Alberta, 2006; Cancer Incidence in Sweden, 2006; Cancer Registry of Tunisia, 2004-2006; Cancer Registry of Casablanca, 2005–2007; Cancer Incidence in Jordan 2005; Bélot et al., 2008; Cancer Registry of Algeria; 2006; Cancer Registry of Egypt- Aswan, 2008)

**Table 1.** Numbers, crude and age-standardized incidence rates of female breast cancer in Morocco, 2004–2008.

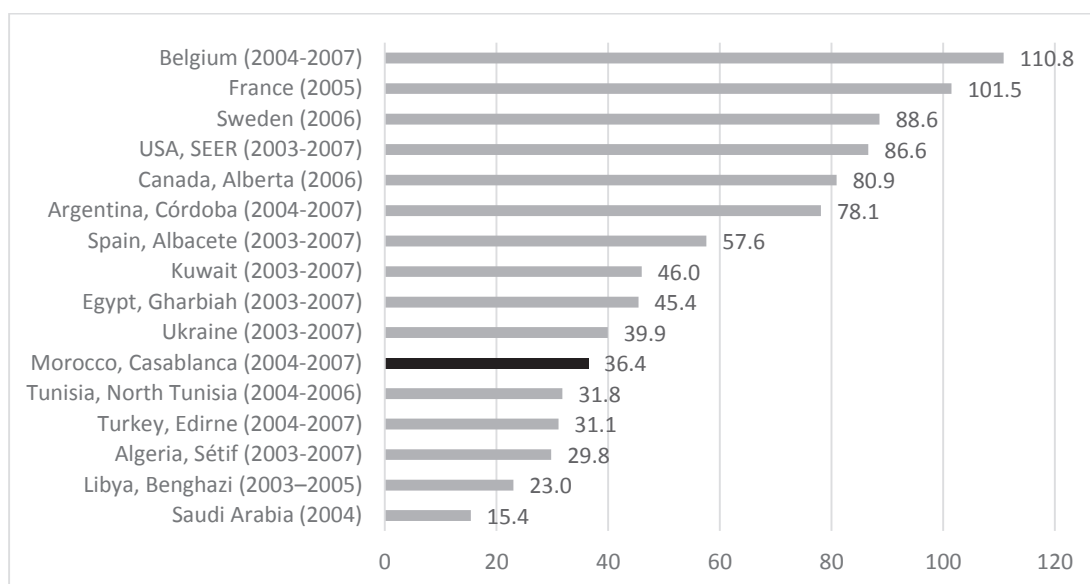
	2004		2005		2006		2007		2008	
	Casablanca	Rabat	Casablanca	Rabat	Casablanca	Rabat	Casablanca	Rabat	Casablanca	Rabat
<b>Cases</b>	662	-	666	127	690	158	763	182	-	151
<b>Crude rate</b>	36.1	-	35.9	38.8	36.3	47.9	39.9	54.7	-	45.1
<b>ASR (M)</b>	-	-	30.4	30.6	31.5	37.8	34.6	43.2	-	35.2
<b>ASR (W)</b>	35.0	-	35.1	35.8	35.4	43.1	38.6	48.1	-	39.0

CR: Crude rate per 100 000.

ASR (M): Age standardized rate (Morocco population) per 100 000.

ASR (W): Age standardized incidence rate (World population) per 100 000.

Data from: The cancer registries of Casablanca and Rabat.



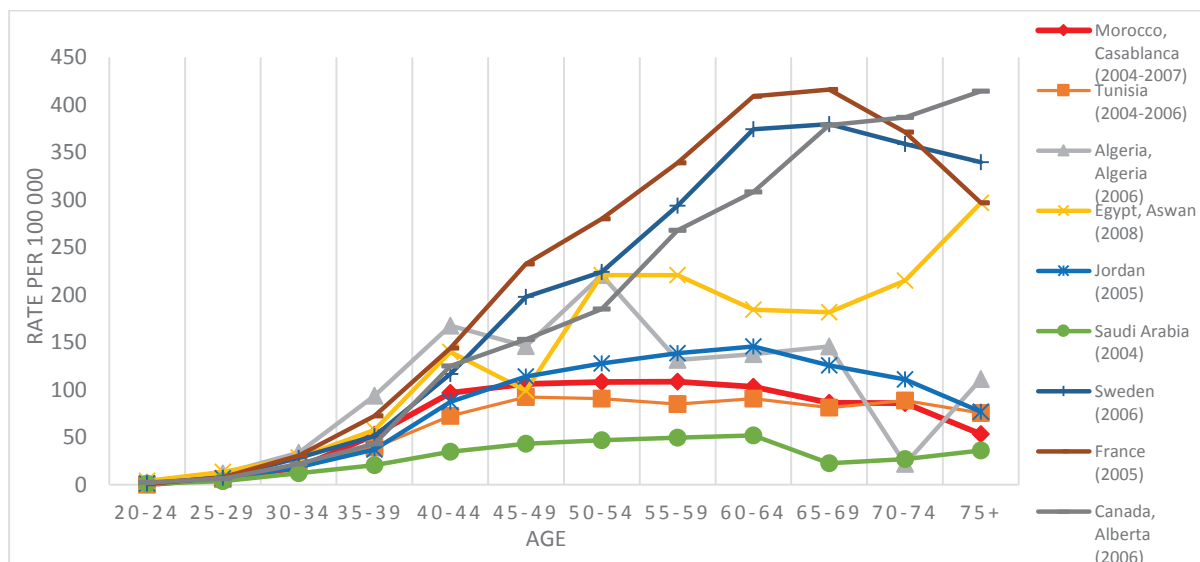
**Fig. 3.** Age-standardized incidence (World population) rate for female breast cancer in Morocco compared to other countries.

Data from: (Forman et al., 2014; Cancer Registry of Saudi Arabia, 2004; El Mistiri et al., 2015; Cancer Registry of Tunisia, 2004-2006; Cancer Registry of Casablanca, 2004, 2005-2007; Cancer Registry of Canada- Alberta, 2006; Cancer Incidence in Sweden, 2006; Bélot et al., 2008).

**Table 2:** Age-specific incidence rate for breast cancer in Moroccan women (2005-2007) according to the cancer registry of Casablanca.

Age range	Incidence rates
20-24	0.5
25-29	6.8
30-34	18.1
35-39	52.8
40-44	96.8
45-49	106.1
50-54	108.2
55-59	108.5
60-64	103.2
65-69	86.5
70-74	85.9
75+	53.2





**Fig. 4:** Age-specific incidence rate for female breast cancer in Morocco (Cancer registry of Casablanca 2005-2007) compared to other countries.

**Table 3:** Breast cancer mortality per 100 000 estimated by Globocan 2012.

Country	Cases	Crude Rate	ASR (W)
Morocco	2878	17.3	18.0
Algeria	2839	15.7	17.5
Tunisia	624	11.6	10.8
Libya	223	6.9	8.4
Egypt	7161	17.1	19.2
Jordan	426	13.6	21.8
Kuwait	103	8.8	17.3
Lebanon	599	27.3	24.0
Saudi Arabia	795	6.2	9.1
China	47984	7.3	5.4
Spain	6075	25.7	11.8
Belgium	2523	45.9	20.3
France	11933	36.7	16.4
Sweden	1450	30.5	13.4
Canada	4924	28.2	13.9
United States of America	43909	27.5	14.9

Data from: Ferlay et al., 2013.

## Discussion

This study provides incidence and mortality rates of breast cancer among Moroccan women, based on the latest available data.

Breast cancer was the leading tumor in Moroccan women accounting for 34.3% of all female cancers registered between the years 2005 and 2007. This proportion was approximately similar to that in Tunisia, and was higher than those in Libya and Saudi Arabia (Fig. 2).

The age-standardized incidence (World) of breast cancer in Morocco (36.4) was higher than that in neighboring countries such as Algeria (29.8), Tunisia (31.8) and Libya (23.0), but was lower than those of some western countries such as France (101.5), USA (86.6) and Canada (80.9) (Fig. 3). This disparity in incidence rates may be due to differences in the distribution of the prevalence of risk factors associated with breast cancer, as well as the availability of early detection in these countries.

Between 2004 and 2008, the incidence of breast cancer in Morocco increased by 2.8% per year. It was close to that reported by central Tunisia registry (2.2% per year) for the period 1993–2006. But such an increase is higher than the one observed in France (1.2% per year) in the period of 1990–1999 before screening was implemented (Corbex et al., 2014).

Several studies suggest that the increasing incidence trend in low- and middle income countries is largely due to increases in risk factors associated with economic development and urbanization, including obesity, adaptation of a Western-type diet, physical inactivity, delayed childbearing and/or having fewer children, earlier age at menarche, and shorter duration of breastfeeding (Boyle and Howell, 2010; DeSantis et al., 2015; Porter, 2008).

During the past several decades, Morocco, like most developing countries, has witnessed sociodemographic changes, cultural and economic transformation. This transformation has also brought many lifestyle changes, such as an increase in the age of marriage and first pregnancy, a decrease in the duration of breastfeeding and fertility, an increase in the prevalence of overweight and obesity, an increase in the prevalence of oral contraceptive use and changes in dietary habits. For example, the mean age at marriage of Moroccan women increased from 18.5 years in 1987 (Ministry of health, Morocco, 1989) to 26.3 years in 2011 (Ministry of health, Morocco, 2011), the total fertility rate (number of children per woman) decreased from 5.9 births per woman in 1980 (Ministry of health, Morocco, 1989) to 2.6 births per woman in 2011 (Ministry of health, Morocco, 2011), the average duration of breastfeeding decreased from 17.5 months in 1980 (Ministry of health, Morocco, 1989) to 16.3 months in 2011 (Ministry of health, Morocco, 2011), the prevalence of overweight among Moroccan women increased from 29.0% in 1999 to 47.8% in 2000 (Toselli et al., 2014) and the prevalence of oral contraceptive use increased from 22.9% in 1987 (Ministry of health, Morocco, 1989) to 48.4% in 2011 (Ministry of health, Morocco, 2011).

Few epidemiological studies have explored risk factors for breast cancer in Moroccan women. A case–control study developed in the region of Rabat reported that early menarche, late menopause, oral contraceptive and family history of breast cancer were likely associated with breast cancer risks (Laamiri et al., 2015). Another study conducted in the region of Oujda

found an inverse relationship between breastfeeding and breast cancer (Maamri et al., 2012). Further studies are required to explore the risk factors of breast cancer among Moroccan women.

Other possible contributing factors to the observed change in breast cancer incidence in Morocco are improved access and availability of healthcare facilities as well as increased awareness regarding breast cancer.

An organized screening, which usually results in a temporary increase in incidence rates, is not implicated in the increase of breast cancer incidence in Morocco between 2004 and 2008. It started after this period (2010). However, the absence of organized screening program in this period may explain partly the incidence difference between Morocco and other countries. According to a World Health Organization study conducted on Moroccan population in 2003, only 2.1% of women aged 40 years or older had a clinical breast examination (or screening mammogram) in their life (Ministry of health, Morocco, 2007).

Regarding the age specific incidence pattern, the lowest rates of incidence of female breast-cancer were seen in the age group 20-29 years and the highest in the age group 50-60 years. This situation was similar in Egypt but it was different from that in some Western countries such as France and Canada (the highest incidence rates of female breast cancer were registered in women above 60 years) (Fig. 4). The difference observed in age specific incidence between Moroccan and Western women may be partly related to the age distribution of populations in those countries. In addition, comparisons between women in high-income countries and middle-income countries should be carefully age-matched (Harford, 2011). Other studies suggest that the variation in genetic marker distribution between North African and Western populations may be involved (Boder et al., 2011).

Overall, like Arab populations (Chouchane et al., 2013; Najjar and Easson, 2010), the average age at presentation of breast cancer in Moroccan women is earlier than in Western countries. Retrospective studies focused on breast cancer in young Moroccan women, reported that 8.0% (Abahssain et al., 2010), 18.6 (Znati et al., 2014), 25.4 % (Boufettal et al., 2010) of the cases were aged 35 years or younger.

There is evidence suggesting that cancer stage is considered the most important factor in determining the prognosis of most cancers (Jazayeri et al., 2015), and women with early-stage breast cancers are expected to have excellent survival rates (Iqbal et al., 2015). Unfortunately a very high proportion of cases in developing countries including Morocco are detected in late stages (Amadou et al., 2014; Kim et al., 2015; Mathew et al., 2016; Schlichting et al., 2015). This is in contrast to that in Western countries, for example in the United States about 80 % of breast cancer cases are diagnosed at an early stage (Mobley and Kuo, 2015). Several reasons are given for the advanced stage at presentation in developing countries, such as the stigma of breast cancer and the societal implications associated with its treatments especially for mastectomy, availability and quality of primary health care services and the lack of access to mammography (Iqbal et al., 2015; Shulman et al., 2010).

Regarding mortality data, in 2012, the breast cancer mortality rate for Moroccan women (18.0 per 100 000) was similar to that in some countries with a middle income, e.g. Algeria (17.5 per

100 000), Egypt (19.2 per 100 000), and Jordan (21.8 per 100 000), but was higher than the world average which was 12.9 per 100 000. Early breast cancer detection, breast cancer diagnosis and management, as well as improved treatments may explain some of the international differences in breast cancer mortality. Furthermore, there are ongoing efforts to understand the genetic and biologic differences that might affect disease outcomes in lower-resource countries (Porter, 2009).

The Moroccan Ministry of Health and the Lalla Salma Foundation for Cancer Prevention and Treatment, launched on March 24, 2010 the National Cancer Prevention and Control Plan (NCPCP), in order to reduce the morbidity and mortality from cancer and to improve the quality of life for patients. Since the implementation of the NCPCP, national-scale operations of breast cancer screening have been regularly carried out everywhere throughout the Kingdom, and early diagnosis services for breast cancer are already available in all reference centers of reproductive health. The target population for breast cancer screening in Morocco is women aged from 45 to 69 years, or women with a family history of breast cancer (grandmother, mother, aunt, sister) (Lalla Salma Foundation for Cancer Prevention and Treatment, 2011). Further studies are needed to explore the impact of this program on breast cancer incidence and mortality in Moroccan women.

In conclusion, although the incidence of female breast cancer in Morocco is lower than Western countries, evidence shows that breast cancer in Moroccan women is rising. This increase of breast cancer incidence has been observed in parallel with reproductive behavior changes and adoption of a Western lifestyle. Further studies are recommended to explore the determinants of breast cancer in Moroccan women. In addition, information regarding survival and mortality of breast cancer need to be collected to guide decision makers to improve breast cancer management in Morocco.

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## **2. Facteurs hormonaux et reproductifs et risque de cancer du sein chez les femmes de la région de Fès, Maroc**

### **2.1. Introduction**

Le cancer du sein est le cancer le plus fréquent chez les femmes à l'échelle mondiale. Il représente 24,2 % des cas de cancers féminins, avec environ 2.1 million nouveaux cas estimés en 2018 [13]. Son incidence est en augmentation dans plusieurs pays du monde, notamment dans certains pays en voie de développement [15,83].

De nombreux facteurs sont identifiés comme étant impliqués dans l'étiologie de cancer du sein à savoir les facteurs hormonaux et reproductifs, comportementaux, génétiques et environnementaux [26,85,86]. Les facteurs hormonaux et reproductifs sont généralement les plus établis dans la littérature et les plus fortement associés au risque de cancer du sein [87,88]. Plusieurs études épidémiologiques explorant le rôle des facteurs hormonaux et reproductifs dans la survenue de cancer du sein ont été menées à travers le monde. Leurs résultats montrent que l'âge précoce de la ménarche, l'âge tardive à la ménopause, la nulliparité ou le faible nombre des grossesses menées à terme, l'âge tardif à la première grossesse, la courte durée ou l'absence d'allaitement, l'utilisation des contraceptifs oraux ainsi que le traitement hormonal substitutif de la ménopause, peuvent augmenter le risque de cancer du sein chez la femme [89,90,91].

La transition socioéconomique rapide qu'a connu le Maroc au cours des dernières décennies s'est accompagnée de changements radicaux dans les comportements reproductifs « profile reproductif » des femmes marocaines [92]. En effet, le nombre moyen d'enfants par femme a chuté d'environ 5,9 enfants en 1980 à 2,2 enfants en 2014 [1,93], l'âge au premier mariage chez les femmes est passé de 18,5 ans en 1987 à 26,3 ans en 2011 [93,94], la durée moyenne de l'allaitement maternel a légèrement baissé, passant de 17,5 mois en 1980 à 16,3 mois en 2011 [93,94]. Enfin, la prévalence de la contraception orale a augmenté de 22,9 % en 1987 à 48,4 % en 2011 [93,94].

Ces changements dans le profile reproductif de la femme marocaine, qui sont généralement à la base de l'étiologie de cancer du sein, peuvent expliquer en grande partie l'augmentation du taux d'incidence du cancer du sein dans ce pays. Malheureusement, les données sur l'association entre les facteurs reproductifs et le risque de cancer du sein dans le contexte marocain sont très rares et les études précédemment réalisées sur ce sujet présentent certaines limites méthodologiques [95,96].

L'objectif de ce chapitre était d'explorer l'association entre les facteurs hormonaux et reproductifs et le risque de cancer du sein chez les femmes de la région de Fès, Maroc.

### **2.2. Méthodes**

Les analyses de ce chapitre ont été réalisées à partir des données collectées dans le cadre de l'étude "Fez Breast Cancer Study".

Les informations détaillées ont été recueillies sur les facteurs hormonaux et reproductifs (âge aux premières règles, longueur de cycle menstruel, statut ménopausique, âge à la ménopause,



nombre d'enfants, nombre de grossesses menées à terme, fausses couches, avortements provoqués, âge à la première grossesse, allaitement maternel, prise des contraceptifs oraux et des traitements hormonaux de la ménopause...) et sur d'autres facteurs de risque de cancer du sein.

Les Odds Ratios et leurs Intervalles de Confiance (ICs) à 95% étaient estimés à partir de régressions logistiques conditionnelles, en ajustant sur les variables de confusion.

### **2.3. Principaux résultats**

Un âge jeune à la ménarche était associé à une augmentation de risque de cancer du sein chez les femmes de notre étude ( $\leq 13$  ans versus  $> 13$  ans ; OR = 1,60, IC 95%: 1,08–2,38 ;  $p = 0,02$ ). La nulliparité était également associée à un risque élevé de cancer du sein (femmes nullipares versus femmes ayant au moins un enfant ; OR = 3,77, IC 95%: 1,98–7,30 ;  $p < 0,01$ ). En revanche, l'âge précoce à la première grossesse à terme était significativement associé à un risque réduit de cancer du sein ( $< 20$  ans versus  $\geq 20$  ans ; OR = 0,41, IC 95%: 0,25–0,65 ;  $p = 0,01$ ).

Les autres facteurs hormonaux et reproductifs n'étaient pas significativement associés au risque de cancer du sein dans cette étude.

### **2.4. Forces et faiblesses de l'étude**

Cette étude comporte certaines limites et sources potentielles de biais et ses résultats doivent être interprétés avec précaution. La principale limite de cette étude concerne la puissance statistique, pour certaines catégories de variables où le nombre de sujets est très faible, la précision n'était donc pas optimale, et le rôle du hasard ne peut pas être entièrement écarté. Le manque de puissance statistique pourrait expliquer pourquoi certaines associations n'ont pas été détectées. Comme d'autres études cas-témoins, la plus part des données de cette étude ont été reportées d'une manière rétrospective, ainsi le biais de mémoire ne pouvait pas être exclu (en particulier pour l'âge aux premières règles). Toutefois, nous pensons que l'utilisation de questionnaires standardisés administrés par des enquêteurs formés pour cette étude a probablement réduit l'effet de ce biais. De plus, nous pensons que ce biais, s'il existe, a été non-différentiel entre les cas et les témoins. Par ailleurs, la proportion des femmes provenant de milieu rural et ainsi que les femmes ayant un niveau socioéconomique bas (estimé par le revenu mensuel du ménage) étaient plus élevée chez les cas que chez les témoins. Cependant, la possibilité d'existence d'un biais de sélection ne peut pas être exclue dans cette étude. Ceci, était l'une des raisons pour laquelle nous avons réalisé par la suite une deuxième étude cas témoins "BreCaFes Study" avec un appariement sur le milieu de résidence.

Malgré les limites de cette étude en particulier sa puissance statistique limitée, elle a permis pour la 1<sup>ère</sup> fois de mieux comprendre les facteurs de risque hormonaux et reproductifs liés au cancer du sein chez les femmes dans cette région du Maroc. En outre, le recrutement des cas de cette étude a été effectué au centre d'oncologie de Fès, qui est un centre de soins tertiaires prenant en charge tout type et tout stade de cancers du sein. De ce fait, la probabilité d'être admis dans ce centre d'oncologie n'est pas, à priori, liée à l'exposition aux facteurs étudiés.

## **2.5. Conclusion**

Cette étude a examiné le lien entre les facteurs hormonaux et reproductifs et le risque de cancer du sein chez les femmes marocaines dans la région de Fès. Les résultats de cette étude suggèrent que l'âge précoce de la ménarche et la nulliparité augmentent le risque de cancer du sein, tandis que l'âge précoce à la première grossesse à terme est associé à une diminution de ce risque. Ce travail a permis de déterminer les facteurs reproductifs qui favorisent la survenue de cancers du sein sur lesquels il est possible d'agir, et cela facilitera par conséquent la mise en œuvre de stratégies efficaces de prévention de cette maladie dans notre pays. Par ailleurs, les résultats de cette étude doivent être interprétés avec précaution et des études épidémiologiques avec large puissance statistique sont requises pour la confirmation de nos résultats.

## 2.6. Article 2

### Menstrual and reproductive factors and risk of breast cancer: A case-control study in the Fez region, Morocco

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**Short title:** Reproductive Factors and Breast Cancer in the Fez Region, Morocco

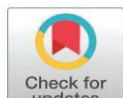
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RESEARCH ARTICLE

### Menstrual and reproductive factors and risk of breast cancer: A case-control study in the Fez region, Morocco

Mohamed Khalis<sup>1,2,3\*</sup>, Barbara Charbotel<sup>2</sup>, Véronique Chajès<sup>4</sup>, Sabina Rinaldi<sup>4</sup>, Aurélie Moskal<sup>4</sup>, Carine Biessy<sup>4</sup>, Laure Dossus<sup>4</sup>, Inge Huybrechts<sup>4</sup>, Emmanuel Fort<sup>2</sup>, Nawfel Mellas<sup>5</sup>, Samira Elfakir<sup>1,3</sup>, Hafida Charaka<sup>1,3</sup>, Chakib Nejjari<sup>1,6</sup>, Isabelle Romieu<sup>4</sup>, Karima El Rhazi<sup>1,3</sup>



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## Abstract

**Background:** Breast cancer is the most common cancer in women worldwide. In the Moroccan context, the role of well-known reproductive factors in breast cancer remains poorly documented. The aim of this study was to explore the relationship between menstrual and reproductive factors and breast cancer risk in Moroccan women in the Fez region.

**Methods:** A case–control study was conducted at the Hassan II University Hospital of Fez between January 2014 and April 2015. A total of 237 cases of breast cancer and 237 age-matched controls were included. Information on sociodemographic characteristics, menstrual and reproductive history, family history of breast cancer, and lifestyle factors was obtained through a structured questionnaire. Conditional logistic regression models were used to estimate odds ratios and 95% confidence intervals for breast cancer by menstrual and reproductive factors adjusted for potential confounders.

**Results:** Early menarche (OR=1.60, 95% CI: 1.08–2.38) and nulliparity (OR=3.77, 95% CI: 1.98–7.30) were significantly related to an increased risk of breast cancer, whereas an early age at first full-term pregnancy was associated with a decreased risk of breast cancer (OR=0.41, 95% CI: 0.25–0.65).

**Conclusion:** The results of this study confirm the role of established reproductive factors for breast cancer in Moroccan women. It identified some susceptible groups at high risk of breast cancer. Preventive interventions and screening should focus on these groups as a priority. These results should be confirmed in a larger, multicenter study.

**Key words:** Breast neoplasms; Reproductive factors; Case-control studies; Fez; Morocco

**Abbreviations:** BMI: Body mass index; GPAQ: Global Physical Activity Questionnaire; MET: Metabolic equivalent; OR: odds ratios; CI: confidence interval.

## Introduction

Breast cancer is the most commonly diagnosed cancer in women worldwide [1]. The etiology of female breast cancer is multifactorial, and includes reproductive, genetic, lifestyle, and environmental factors [2–5].

In North Africa, as in many regions that are either developing or in epidemiological transition, breast cancer incidence rates have clearly risen [6]. In Morocco, breast cancer remains the most common cancer in women, constituting about 35.8% of all new cancer diagnoses in women [7]. According to the most recent report of the cancer registry in Casablanca, the age-standardized incidence rate of breast cancer increased from 35.0 to 49.5 per 100 000 women between 2004 and 2012, showing an annual increase of 3.18%. The most widely proposed explanations for this increase are changes in reproductive behaviors (smaller number of children, shorter duration of breastfeeding, higher age at first pregnancy), and in lifestyle and

dietary habits (higher obesity rates) among Moroccan women in the past three decades [8–10].

Numerous epidemiological studies performed throughout the world have confirmed the role of many reproductive factors, such as age at menarche, age at first pregnancy, age at menopause, parity, and breastfeeding, in the etiology of breast cancer [2,11,12].

However, evidence suggests that international variation in the burden of breast cancer reflects differences in the patterns of risk factors [13]. In the Moroccan context, the role of well-known reproductive factors in breast cancer remains poorly documented, and it is probable that unidentified exposures specific to Moroccan women may play an important role.

The aim of this case–control study was to explore the relationship between menstrual and reproductive factors and breast cancer risk in Moroccan women in the Fez region. To the best of our knowledge, this is one of the first epidemiological studies on risk factors for breast cancer in Morocco.

## **Methods**

### *Study design and setting*

The Fez Breast Cancer Study is a case–control study, conducted at the Hassan II University Hospital of Fez, ranked as one of the most important medical centers in Morocco, covering more than 3 million people in the Fez region.

In this study, a total of 474 women (237 cases and 237 age-matched controls) were recruited between January 2014 and April 2015.

### *Study subjects*

Cases were patients recently diagnosed with histologically confirmed breast cancer (all consecutive cases), admitted during the study period to the Medical Oncology Center at the University Hospital of Fez, which is a referral center for breast cancer in the region.

Controls were healthy women with no history of cancer, who accompanied patients to the consultations department at the University Hospital of Fez. This department provides health consultations to patients for various medical and surgical specialties. Women who accompanied patients with any type of cancer were excluded from this study. Control subjects were individually matched to cases by age (age at cancer diagnosis  $\pm$  3 years), and they were recruited at approximately the same time as the recruitment of cases.

Because of the difficulty of recruiting some controls aged 60 years or older among the women accompanying patients to the hospital, women randomly selected at the consultations department were asked whether they could provide the telephone numbers and addresses of other, older women, who could potentially be recruited. Women meeting the age requirement were called by telephone, checked for inclusion criteria, and invited to participate in this study. The socioeconomic characteristics such as income and education level of controls recruited with this method are approximately the same as those of other controls (data not shown).

The participation rate in this study was 97.1% (237/244) for cases and 92.5% (237/256) for controls.

#### Ethical considerations

This study was approved by the Ethics Committee of the Hassan II University Hospital of Fez. Participation in this study was strictly voluntary, and all subjects were informed about the right to withdraw at any time without giving an explanation. All information collected from participants was kept confidential. The Fez Breast Cancer Study was conducted according to the guidelines of the Declaration of Helsinki. Written informed consent to participate in the study was obtained from all study participants before the interviews were conducted.

#### Data collection and measurements

Data were collected through face-to-face interviews by six trained interviewers. The pre-tested structured questionnaire included information on sociodemographic characteristics (e.g., age, educational level, marital status, area of residence, occupation, monthly household income), menstrual and reproductive history (e.g., age at menarche, regularity of menstrual cycle, age at menopause, parity, age at first full-term pregnancy, history of abortions, history of miscarriages, use of oral contraceptives, breastfeeding, postmenopausal hormone use), family history of breast cancer in first- and second-degree relatives, alcohol consumption, smoking, and passive smoking (the inhalation of tobacco smoke from people who are smoking nearby in the home or at work).

Current weight and height were measured by the interviewers according to the recommendations of Lohman et al. (1988) [14]. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters. BMI was classified using cut-off points recommended by WHO [15]. The categories underweight ( $<18.5 \text{ kg/m}^2$ ) and normal weight ( $18.5\text{--}24.9 \text{ kg/m}^2$ ) were grouped into one category ( $<25 \text{ kg/m}^2$ ), due to the low number of women in these categories. Information on physical activity was obtained using a Global Physical Activity Questionnaire (GPAQ2), which includes estimates of physical activity in three domains (activity at work, activity travelling to and from places, recreational activities) as well as sedentary behavior [16]. Definitions of these three domains are given in (WHO 2016) [16]. The Metabolic Equivalent (MET)-minutes per week were calculated based on the published GPAQ Analysis Guide [16]. The intensity of physical activity was classified into three categories: light intensity ( $<600 \text{ MET-minutes per week}$ ), moderate intensity ( $600\text{--}3000 \text{ MET-minutes per week}$ ), and vigorous intensity ( $\geq 3000 \text{ MET-minutes per week}$ ).

To determine menopausal status at recruitment, women were considered to be premenopausal if they reported regular menstrual cycles over the previous 12 months and postmenopausal in case of absence of menstruation in the last 12 months. Women who had missing data on menopausal status were considered to be premenopausal if they were younger than 45 years, and postmenopausal if they were older than 54 years, because in a previous study conducted in Moroccan women, the median age at menopause was estimated to be 50.25 years [17]. Women in the age range 45–54 years were assigned to an unknown menopausal status.

#### Statistical analysis

Frequencies (percentages) for qualitative variables and mean values ( $\pm$  standard deviation) for continuous variables were calculated. Conditional logistic regression models were used to identify the reproductive factors associated with breast cancer. Multivariate adjusted odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were estimated, adjusting for area of residence (urban, rural), monthly household income ( $\leq 2000$ ,  $>2000$  Moroccan Dirham), age at menarche (continuous), menopausal status and age at menopause combined (premenopausal, postmenopausal  $<46.5$  years, postmenopausal  $\geq 46.5$  years, missing), parity (parous, nulliparous), age at first full-term pregnancy (nulliparous,  $<20$  years,  $\geq 20$  years), family history of breast cancer (yes/no), and BMI ( $<25$ ,  $25\text{--}29$ ,  $\geq 30$  kg/m<sup>2</sup>). None of other potential confounders listed in Table 1 changed our risk estimates by 10% or more. Median values in controls were used as cut-off points for age at menarche, age at menopause, age at first full-term pregnancy, and breastfeeding per child. BMI information was missing for three controls, and these missing values were replaced with the median value in controls. Data analysis was performed using Stata/IC 14.1 software.

## Results

Table 1 presents the baseline characteristics of the subjects by case–control status. The mean age of the study population (cases and controls) was 48.6 years. Compared with control subjects, cases were more likely to be postmenopausal, nulliparous, younger at menarche, and older at first pregnancy, to live in a rural area, and to have a higher BMI, a family history of breast cancer, a lower monthly household income, and a longer interval between age at menarche and age at first full-term pregnancy. Cases and control subjects did not show differences in marital status, educational level, occupation, passive smoking, intensity of physical activity, age at menopause, breastfeeding per child, or interval between age at menarche and age at menopause.

**Table 1. Baseline characteristics of case and control subjects [number (percentage) or mean  $\pm$  standard deviation].**

Characteristics		Cases	Controls
		(n = 237)	(n = 237)
<b>Age at recruitment (years)</b>			
	<40	52 (21.9)	48 (20.3)
	40–49	72 (30.4)	80 (33.8)
	50–59	70 (29.5)	68 (28.7)
	$\geq 60$	43 (18.1)	41 (17.3)
<b>Area of residence</b>			
	Urban	161 (67.9)	183 (77.2)
	Rural	76 (32.1)	54 (22.8)
<b>Marital status</b>			
	Single	34 (14.3)	17 (7.2)

	Married	153 (64.6)	173 (73.0)
	Divorced	23 (9.7)	16 (6.8)
	Widowed	27 (11.4)	31 (13.1)
<b>Educational level</b>			
	Illiterate	151 (63.7)	153 (64.5)
	Elementary school	44 (18.6)	38 (16.0)
	Secondary school	30 (12.6)	30 (12.6)
	High school	10 (4.2)	14 (5.9)
	Unknown	2 (0.8)	2 (0.8)
<b>Monthly household income (MAD)</b>			
	>2000	140 (59.1)	173 (73.0)
	≤2000	97 (40.9)	64 (27.0)
<b>Occupation</b>			
	Housewife	214 (90.3)	211 (89.0)
	Employed	23 (9.7)	26 (11.0)
<b>Menopausal status</b>			
	Premenopausal	100 (42.1)	124 (52.3)
	Postmenopausal	129 (54.4)	106 (44.7)
	Unknown	8 (3.3)	7 (2.9)
<b>Parity</b>			
	Parous	181 (76.4)	201 (84.8)
	Nulliparous	56 (23.6)	36 (15.2)
<b>Family history of breast cancer</b>			
	No	198 (83.5)	224 (94.5)
	Yes	39 (16.5)	13 (5.5)
<b>Passive smoking</b>			
	No	131 (55.3)	139 (58.6)
	Yes	106 (44.7)	98 (41.4)
<b>Intensity of physical activity</b>			
	Light and moderate intensity	158 (66.7)	147 (62.0)
	Vigorous intensity	79 (33.3)	90 (38.0)
<b>Body mass index (kg/m<sup>2</sup>)</b>			
	<25	40 (16.9)	61 (25.7)
	25–29	86 (36.3)	81 (34.2)
	≥30	111 (46.8)	95 (40.1)
<b>Age at menarche (years)</b>		13.7 ± 1.7	14.0 ± 1.8
<b>Age at menopause (years)<sup>a</sup></b>		47.7 ± 5.9	47.2 ± 5.4
<b>Age at first full-term pregnancy (years)</b>		22.2 ± 5.4	20.9 ± 4.9
<b>Interval between age at menarche and age at first full-term pregnancy (years)<sup>b</sup></b>		8.4 ± 5.6	6.8 ± 5.0
<b>Interval between age at menarche and age at menopause (years)<sup>a</sup></b>		33.8 ± 6.5	33.0 ± 5.7



<b>Breastfeeding per child (months)<sup>c</sup></b>	12.0 ± 7.3	12.2 ± 7.1
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MAD: Moroccan Dirham.

<sup>a</sup>Among postmenopausal women; <sup>b</sup>Among parous women; <sup>c</sup>Among breast-feeding women.

Table 2 shows crude and adjusted ORs and 95% CIs for breast cancer by menstrual and reproductive factors. After adjustment for potential confounders, women who reached menarche at age ≤13 years had a significantly higher risk of breast cancer, compared with women who reached menarche after age 13 years (OR=1.60, 95% CI: 1.08–2.38). Nulliparous women had a significantly higher risk of breast cancer compared with parous women (OR=3.77, 95% CI: 1.98–7.30). Women who were younger than 20 years at their first full-term pregnancy had a significantly lower risk of developing breast cancer, compared with women who were older than 20 years at their first full-term pregnancy (OR=0.41, 95% CI: 0.25–0.65). Finally, there was no significant association with breast cancer risk for irregularity of menstrual cycle, age at menopause, history of miscarriages and abortions, breastfeeding per child, or history of oral contraceptive use.

**Table 2. Association between menstrual and reproductive factors and breast cancer risk.**

Characteristics	Cases /controls	Crude OR (95% CI)	Adjusted OR <sup>a</sup> (95% CI)
<b>Age at menarche (years)</b>			
>13	118/145	Reference	Reference
≤13	119/92	1.59 (1.09–2.31)	1.60 (1.08–2.38)
<b>Regularity of menstrual cycle</b>			
Regular	222/223	Reference	Reference
Irregular	15/12	1.20 (0.51–2.77)	1.24 (0.54–2.85)
<b>Age at menopause (years)<sup>b</sup></b>			
<46.5	51/46	Reference	Reference
≥46.5	62/46	1.72 (0.82–3.63)	1.26 (0.69–2.30)
<b>Parity</b>			
Parous	181/201	Reference	Reference
Nulliparous	56/36	1.85 (1.12–3.04)	3.77 (1.98–7.30)
<b>History of miscarriages</b>			
No	166/161	Reference	Reference
Yes	69/76	0.88 (0.61–1.28)	0.96 (0.61–1.51)
<b>History of abortions</b>			
No	208/216	Reference	Reference
Yes	27/21	1.32 (0.71–2.45)	1.59 (0.83–3.04)
<b>Age at first full-term pregnancy (years)</b>			
≥20	117/102	Reference	Reference
<20	63/99	0.56 (0.34–0.92)	0.41 (0.25–0.65)
<b>Breastfeeding per child (months)<sup>c</sup></b>			

	<11	86/93	Reference	Reference
	≥11	86/94	0.90 (0.53–1.51)	1.0 (0.52–1.93)
<b>History of oral contraceptive use</b>				
	No	89/92	Reference	Reference
	Yes	148/145	1.05 (0.71–1.54)	1.11 (0.74–1.66)

OR: odds ratio; CI: confidence interval.

<sup>a</sup>Odds ratios adjusted for area of residence (urban, rural), monthly household income (≤2000, >2000 Moroccan Dirham), age at menarche (continuous), menopausal status and age at menopause combined (premenopausal, postmenopausal <46.5 years, postmenopausal ≥46.5 years, missing), parity (parous, nulliparous), age at first full-term pregnancy (nulliparous, <20 years, ≥20 years), family history of breast cancer (yes/no), and body mass index (<25, 25–29, ≥30 kg/m<sup>2</sup>); <sup>b</sup>Among postmenopausal women; <sup>c</sup>Among breastfeeding women.

## Discussion

The purpose of this study was to explore the relationship between menstrual and reproductive factors and breast cancer risk among Moroccan women in the Fez region.

The results from this case-control showed that early menarche ( $\leq 13$  years) and nulliparity were significantly associated with an increased risk of breast cancer, whereas an early age at first full-term pregnancy ( $< 20$  years) was associated with a significantly decreased risk of breast cancer.

Consistent with findings from other epidemiological studies in Morocco [18] and other countries [19–22], we found a significant association between early age at menarche and an increased risk of breast cancer. A meta-analysis of 117 epidemiological studies confirmed that young age at menarche is associated with increased risk of breast cancer [23]. This meta-analysis showed that for every year of younger age at menarche, breast cancer risk increased by a factor of 1.05 (95% CI: 1.04–1.05). The biological explanation for this association is based on the early and prolonged exposure of the breast epithelium to estrogens produced during the period of activity of the ovaries [24].

In most studies in the literature, nulliparity was one of the strongest risk factors for breast cancer [21,25,26]. In line with these studies, we also found a positive association between nulliparity and breast cancer risk. Several mechanisms have been proposed to explain the potential protective effect of pregnancy on breast cancer, such as decreased levels of estrogen and progesterone, increased levels of sex hormone-binding globulin, and pregnancy-induced differentiation of breast tissue [27,28]. Further investigations are needed to explore the mechanisms underlying the positive association between nulliparity and breast cancer risk reported in our study.

In addition, a decrease in breast cancer risk with an increasing number of live births has been reported by many studies [29–32]. Clavel-Chapelon and Gerber indicated that each full-term pregnancy leads to a 3% reduction in the risk of breast cancer diagnosed early or in premenopausal women, while this reduction reaches 12% for cancers diagnosed in postmenopausal women [33].

In our study, an early age at first full-term pregnancy was associated with a reduced risk of breast cancer. Women who were younger than 20 years at first full-term pregnancy had a significant decreased risk of breast cancer compared with women who were older than 20 years. This finding may be explained by the fact that, at the first birth, the mammary epithelial cells, which have a high degree of terminal differentiation, are capable of metabolizing carcinogens and can repair DNA damage more efficiently [28]. Our results were in line with the findings of previously published studies in other populations [26,29,34,35].

There is evidence suggesting that breastfeeding may have a protective effect on breast cancer risk [36]. A meta-analysis including 50 302 women with breast cancer and 96 973 controls found that the relative risk of breast cancer decreased by 4.3% for every 12 months of breastfeeding [36]. Other studies also supported the inverse relationship between breastfeeding and breast cancer [25,37–39]. In our study, there is a lack of significant association between breastfeeding and breast cancer risk. This may be related to the

prolonged breastfeeding practiced by both cases and controls in our study population and, more generally, in the region. The distinct exposure pattern of our population should be considered in the interpretation. In this study, we assessed the relationship between breastfeeding and breast cancer risk without considering hormone receptor status. Some studies have suggested that the effect of breastfeeding may differ by breast cancer subtypes [40–43]. Therefore, further studies are required to explore probable differences by tumor subtypes in our population.

A late age at menopause is a well-established risk factor for breast cancer [12]. Numerous studies [22,30,34,44] have shown a significant association between a later age at menopause and increased risk of breast cancer, while other studies, including ours, failed to report a significant association [19,45]. The higher risk of developing breast cancer in women with a late age at menopause may be explained by both longer duration of and higher level of exposure to estrogen and progesterone experienced by these women [12].

In agreement with results from another case–control study in the region [20], our study did not find a statistically significant association between oral contraceptive use and risk of breast cancer. However, some previous studies found that oral contraceptive use was associated with an increased risk of breast cancer [46,47]. Age at starting oral contraceptive use might be determinant in the association between oral contraceptive use and breast cancer risk; however, we did not have information on that variable, so we were unable to further assess its effect in our study.

The relationship between history of abortions and breast cancer risk is controversial [48]. In the current study, we found that history of abortions is not significantly associated with breast cancer risk. This result is in line with a meta-analysis of 53 epidemiological studies, including 83 000 women with breast cancer from 16 countries [49]. However, a recent meta-analysis conducted in China reported a positive association between breast cancer risk and induced abortion [50]. More details about abortion (number, age at abortion) may provide important information on the relationship between abortion and breast cancer risk.

Our study has some limitations. First, due to the retrospective nature of this study, most of our data were self-reported by women, and could be subject to recall bias. However, women were not aware of potential risk factors for breast cancer, and therefore measurement error is most likely to be random (non-differential misclassification). Another limitation is the relatively small number of cases and controls, which impaired stratified analysis by menopausal status, and factors with small effect on breast cancer risk may have been missed because of low statistical power. In addition, considering that cases were significantly more likely to live in a rural area and to have a lower monthly household income, compared with controls, the possibility of selection bias cannot be ruled out in this study.

The probable explanation is that controls were recruited from a consultations department located in an urban area, and those accompanying patients to this department are more likely to reside in an urban area and consequently their socioeconomic status may have been relatively high. The epidemiological transition and the rise of chronic diseases associated with urban lifestyles that are beginning to be seen among Moroccan women of lower

socioeconomic status may be another possible explanation for this difference. It is therefore particularly important to explore the relationship between the socioeconomic level and breast cancer risk in the Moroccan context.

Moreover, in this study some variables were excluded from the analysis, due to the low number of women with certain habits in the region of the study (the frequency of postmenopausal hormone use was 1.68% in cases and 0.84% in controls, the frequency of smoking was 4.64% in cases and 0.42% in controls, and the frequency of alcohol consumption was 0.00% in cases and 0.42% in controls).

This study has several strengths, including an age-matched case–control design, a high participation rate in cases and controls, and histological confirmation of breast cancer. Moreover, this is the first epidemiological study to investigate the relationship between reproductive factors and risk of breast cancer in the Fez region.

Our study confirms the role of established reproductive factors for breast cancer in Moroccan women. Studies exploring changes in the pattern of breast cancer risk factors in Morocco [8,10] suggest that adoption of a Western lifestyle, birth-control policies, and changes in dietary habits might have resulted in earlier age at menarche, later age of marriage and first pregnancy, and a decline in fertility.

Finally, the results of this study identified some susceptible groups at high risk of breast cancer. Preventive interventions and screening should focus on these groups as a priority. These results should be confirmed in a larger, multicenter study to support the generalization of the results to all Moroccan women.

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### **3. Score de style de vie et risque de cancer du sein chez les femmes de la région de Fès, Maroc**

#### **3.1. Introduction**

Le cancer du sein constitue un enjeu majeur de santé publique dans plusieurs pays en voie de développement, incluant le Maroc, en raison de la croissance de ses taux d'incidence et de mortalité [16,97]. Sur l'ensemble des cancers survenant dans les deux sexes, le cancer du sein est devenu le cancer le plus fréquent dans les régions du monde les moins développées, alors qu'en 2002, il n'était que le quatrième [92,98].

Le mode de vie adopté par les femmes dans ces populations s'approche progressivement d'un mode de vie plus ou moins occidental (tabagisme, consommation d'alcool, obésité, sédentarité et manque d'activité physique, etc...), suite au développement socioéconomique et à l'urbanisation très rapide que vivaient ces pays. Ceci peut jouer un rôle important dans l'augmentation des taux de morbidité par cancer du sein récemment observé dans ces pays [17,97,99].

Plusieurs facteurs de risque modifiables, en particulier liés au mode de vie, ont été individuellement associés au risque de cancer du sein chez la femme, à savoir l'activité physique [100,101], l'obésité (chez les femmes en post-ménopause) [102,103], la consommation d'alcool [104], le tabagisme [60,61], et facteurs alimentaires [68,105]. Etant donné que les facteurs comportementaux agissent souvent simultanément et d'une manière regroupée [106–108], il est important d'explorer leurs effets conjoints, en complément de leur association individuelle.

Des études récentes ont mis en évidence l'association entre l'effet combiné de facteurs liés à un mode de vie sain, à l'adhésion aux recommandations de santé publique et la diminution de risque de mortalité toutes causes confondues et par cause spécifique [109–111], ainsi que de plusieurs maladies chroniques incluant certains cancers [112–119]. Cet effet protecteur a également été rapporté par plusieurs études portant sur le risque du cancer du sein [120–124].

Cependant, toutes ces études ont été menées dans les pays industrialisés, et il n'existe pas d'information à propos de l'association entre les facteurs de mode de vie combinés et le risque de cancer du sein dans les pays en voie de développement. À notre connaissance, aucune étude antérieure n'a été menée sur ce sujet dans les pays en voie de développement subissant une transition épidémiologique et nutritionnelle comme le Maroc.

L'objectif principal de chapitre était d'étudier l'association entre un score de style de vie sain tel que prédéfini dans la littérature [121] et le risque de cancer du sein chez les femmes de la région de Fès, Maroc.

### **3.2. Méthodes**

Les analyses présentées dans ce chapitre ont été réalisées à partir des données collectées pour l'étude "BreCaFez Study".

Le score de style de vie a été calculé en se basant sur onze composantes liées au mode de vie comprenant la consommation de viande blanche, de viande rouge (ou de viande rouge transformée), de la crème, de fromage, de poisson, de fruits et légumes, d'alcool, l'activité physique, l'indice de masse corporelle (IMC), le tabagisme, et l'allaitement.

Pour chaque participante, nous avons calculé le score de style de vie en attribuant 0 (faible adhésion), 0,5 (moyenne adhésion) ou 1 (forte adhésion) point aux catégories de chaque composante. Le score cumulé variait de 0 (le moins sain) à 11 points (le plus sain).

Les odds ratios et leurs intervalles de confiance à 95% ont été estimés à partir de régressions logistiques conditionnelles et non conditionnelles, en ajustant sur les variables de confusion.

### **3.3. Résultats**

La moyenne de score de style de vie sain était de 8,1 ( $\pm 1,1$ ) chez les cas et de 9,0 ( $\pm 0,9$ ) chez les témoins. Dans les analyses multivariées et après ajustement sur les facteurs de confusion, une augmentation d'un point du score de style de vie sain était significativement associée à une réduction de 56% (IC 95%: 39 – 68% ;  $p < 0,01$ ), 49% (IC à 95%: 30 – 63% ;  $p < 0,01$ ) et 59% (IC à 95%: 40–72% ;  $p < 0,01$ ) du risque de cancer du sein chez toutes les femmes, les femmes en préménopause et les femmes en post-ménopauses, respectivement.

### **3.4. Forces et faiblesses de l'étude**

Certaines limites peuvent être soulignées pour ce travail en plus de celles liées au caractère rétrospectif de l'étude cas témoins citées précédemment dans la partie 4 du Chapitre II. Premièrement, en raison de l'absence de recommandations alimentaires spécifiques à la population marocaine, notre score de style de vie était basé sur des recommandations internationales en matière de santé publique et de prévention du cancer. Cependant, il est nécessaire de développer des recommandations de santé publique spécifiques à la population marocaine pour la prévention de cancer du sein. Deuxièmement, en raison de la puissance statistique limitée, nous n'avons pas été en mesure de tester la contribution spécifique de chaque composant du score dans la réduction du risque de cancer du sein dans notre étude. Troisièmement, étant donné qu'un grand nombre de cas de cancer du sein sont généralement diagnostiqués à des stades avancés au Maroc [55], nous ne pouvons pas exclure l'effet de la maladie sur le changement de certains facteurs de style de vie (exemple, l'activité physique) avant le diagnostic du cancer du sein chez certains cas de notre étude.

Cette étude présente de nombreuses forces. A notre connaissance, cette étude est la première au Nord de l'Afrique ayant évalué le lien entre un score de style de vie sain et le risque de cancer du sein. En outre, nous avons été en mesure de prendre en compte de nombreux facteurs de confusion potentiels dans les analyses. De plus, le recrutement des témoins était réalisé en population générale, et nous supposons que ces témoins sont représentatifs des femmes de notre région. Un autre point fort de cette étude est le taux élevé de participation dans l'étude chez les cas et les témoins.

### **3.5. Conclusion**

Les résultats de cette étude ont montré qu'un score de style de vie sain élevé était associé à une réduction significative du risque de cancer du sein chez les femmes de notre population en pré- et post- ménopause. Cette étude, comme la plupart d'autres études antérieures menées sur ce sujet, a permis de souligner le rôle potentiel de l'effet conjoint des facteurs de style de vie dans le risque de cancer du sein. Par ailleurs, les facteurs de mode de vie doivent être intégrés dans les messages éducatifs et dans les interventions portant sur la prévention du cancer du sein chez les femmes marocaines.

### 3.6. Article 3

#### Healthy lifestyle and breast cancer risk: A case-control study in Morocco.

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#### Healthy lifestyle and breast cancer risk: A case-control study in Morocco

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## Abstract

**Background** Some modifiable risk factors have been independently associated with breast cancer (BC) risk in Moroccan women, but no studies have investigated their joint association. This study aimed to investigate the association between a Healthy Lifestyle Index (HLI) score and BC risk among Moroccan women.

**Methods** In this case–control study, 300 incident BC cases and 300 controls, matched by age and area of residence were recruited. Cases were women newly-diagnosed with histopathologically–confirmed BC at the University Hospital in Fez, Morocco. Controls were randomly selected healthy women recruited from 6 primary health centers in Fez. HLI scores developed within this study were assigned to participants based on 11 factors (red and processed meat, white meat, cream, cheese, fish, fruit and vegetables, physical activity, BMI, smoking, alcohol consumption, and breastfeeding), where 0 was given to unhealthy and 0.5 or 1 to healthy levels of each factor. Conditional and unconditional logistic regression models were used to assess the association between HLI scores and BC risk.

**Results** Mean of HLI scores were 8.1 ( $\pm 1.1$ ) and 9.0 ( $\pm 0.9$ ) in cases and controls, respectively,  $p < 0.01$ . After adjusting for potential confounders, one-point increment in the HLI score was associated with 56% (95% CI, CI: 39–68%), 49% (95% CI: 30–63%), and 59% (95% CI: 40–72%) lower risks of BC in all, premenopausal, and postmenopausal women, respectively.

**Conclusion** High HLI scores were associated with decreased risk of BC in Moroccan women. These findings suggest that BC prevention policies should include strategies for engaging Moroccan women in healthy lifestyles.

**Keywords:** Breast cancer; Health index; Lifestyle; Case–control; Morocco; Developing countries

## Abbreviations

BC, breast cancer; LMIC, low-income and middle-income countries; HLI, healthy lifestyle index; BMI, body mass index; METs, metabolic equivalents; OR, odds ratio; CI, confidence intervals; SD, standard deviation

## 1. Introduction

Breast cancer (BC) is the most common cancer among women worldwide [1]. Although BC incidence rates are still highest in high-income countries [2], in many low- and middle-income countries (LMIC) cancer incidence and mortality rates are rising rapidly. The rising rates are linked to ongoing societal and economic development and lifestyles approaching western lifestyles (e.g. increase in smoking, excess body weight, and physical inactivity) [3]. In Morocco, BC represents a major public health concern as it accounts for 35.8% of all incident female cancers with an age-standardized rates of 49.5/100 000 women [4]. In 2012, 2878 BC deaths were estimated in Morocco [5].

Numerous risk factors for female BC have been identified, including older age, reproductive and hormonal factors (e.g., early menarche, late age at first pregnancy, late menopause, and nulliparity), hereditary predisposition (family history of BC and high-penetrance genetic mutations), high breast density and adult attained height [6–9]. Additionally, there is a considerable evidence that several modifiable lifestyle factors such as physical inactivity [10,11], body fatness (obesity in postmenopausal women) [12,13], dietary factors [14,15], alcohol consumption [16] and tobacco smoking [17,18], are individually associated with the risk of BC. As behavioral factors and lifestyle pattern are often clustered [19–21], it is important to consider these lifestyle factors simultaneously and to take into account their joint effects.

Consistent positive associations have been reported in several studies between healthy behavioral patterns or combined lifestyle factors and lower risk of chronic diseases [22–25], including some cancers [26–30], as well as cause-specific and total mortality [31–33]. The association between combined lifestyle factors and the risk of developing BC has been investigated [34–38], and a healthy lifestyle was related to a decreased risk of BC. In fact, Parkin DM et al. reported that at least 17% of BC cases could be prevented from an overall healthy lifestyle [39]. However, the above BC studies were conducted only among western populations.

In contrast, less information is available on the association of combined lifestyle factors with the risk of BC in developing countries. To the best of our knowledge, no previous studies have investigated this association among women in Morocco. Therefore, it is important to investigate whether the association between these lifestyle factors and BC risk observed in western countries exists in LMIC countries, like Morocco.

The purpose of this study was to investigate the association between a healthy lifestyle index (HLI) score as previously defined [35], including diet, physical activity, body mass index (BMI), smoking, alcohol consumption and breastfeeding combined, and the risk of developing BC in Moroccan women. Based on the findings of previous studies, we hypothesized that a higher HLI score is associated with a lower risk for BC.

## 2. Methods

### 2.1. Study Population

The BreCaFes Study is a case–control study, conducted in the Fez region- Morocco, from February 2016 until August 2017. A total of 300 incident BC cases and 300 controls were recruited in the study.

Incident BC cases were recruited from the Medical Oncology Center of the University Hospital in Fez, which is a referral center for BC for other hospitals in the region. The oncology center receives patients with all types and stages of BC from the entire region of Fez. The inclusion criteria of the cases were: a) newly-diagnosed histologically-confirmed in situ or invasive BC, b) had not received any treatment, such as radiotherapy, chemotherapy or anti-estrogens (e.g., tamoxifen), c) were not suffering from chronic kidney failure, d) were not pregnant or nursing during the study, and e) were able to give informed consent. The response rate for cases was 96.7% (300/310). The reasons for refusal were mainly lack of time for interview or feeling tired.

Controls were randomly selected healthy women with no previous history of cancer, visiting one of six outpatient primary health centers (three urban and three rural) in the Fez region. These centers provide several health services and receive women representative of the general population, in terms of socio-demographic characteristics. Women who accompanied patients with any type of cancer were excluded from this study. Control subjects were matched individually to the cases by age ( $\pm 5$  years) (72% of pairs matched by 1-year age) and area of residence (urban vs. rural). The response rate for controls was 87.9% (300/341). The reasons for refusal were mainly lack of interest or lack of time for interview.

### 2.2. Data collection and measurements

Participants were interviewed at enrolment in the study by four trained and standardized interviewers and data were collected using an in depth questionnaire, including information about sociodemographic characteristics, lifestyle habits, general health, etc. and a detailed dietary questionnaire.

#### The general questionnaire

The general questionnaire collected data on sociodemographic characteristics, occupational history, anthropometric characteristics, family history of cancer including BC, menstrual and reproductive history (e.g., age at menarche, age at first full-term pregnancy, parity, menopausal status, age at menopause, history of breastfeeding), hormone use, smoking, alcohol consumption, and physical activity.

Socio-economic status of participants was assessed using a validated wealth score based on household assets including electricity, television, cell phone, refrigerator, indoor bath or shower, indoor tap, flush toilet, washing machine, car and landline phone [40]. This score was developed and evaluated in eight developing countries including Morocco. The scores were



calculated for each participant by assigning points of 0 or 1 to each asset ownership question. The total score ranges between 0 (low level) and 10 (high level).

To assess physical activity, participants were asked to provide information on the total number of hours spent in occupational, recreational and household physical activity from Monday through Sunday in a typical week that reflects physical activities in the past 12 months. Physical activities were categorized based on their intensity by using metabolic equivalents (METs) values listed in the Compendium of Physical Activities [41]. Intensity was classified into three categories according to guidelines for physical activity [42,43]: light-intensity physical activities with METs <3.0; moderate-intensity physical activities with METs between 3.0 and 5.9; and vigorous-intensity physical activities with METs ≥6.0. Definitions and examples were provided for each intensity level by type of activity. In this study, we used moderate and vigorous-intensity physical activities in hours per week of all activities combined, including occupational, recreational, and household activities.

Current weight and height were measured by interviewers at recruitment according to the recommendations of Lohman et al. [44]. The BMI was calculated as weight (kg) / height<sup>2</sup> (m<sup>2</sup>). Postmenopausal status was defined as self-reported absence of menstruation in the last 12 months.

#### The dietary intake questionnaire

Usual dietary intake of participants during the previous 12 months was assessed using a previously validated Food Frequency Questionnaire [45]. This questionnaire included 255 food items giving details of 32 main Moroccan-specific food groups. For each food item, a standard portion size was given and study subjects were asked to choose from nine frequency response options, ranging from “never” to “six or more times a day”. The reproducibility and validity of this FFQ have been assessed on 105 healthy Moroccan adults, and the results showed a good relative validity (de-attenuated correlations range from 0.24 for fiber to 0.93 for total monounsaturated fatty acids) and a good reproducibility (intra-class correlation coefficient range from 0.69 for fat to 0.84 Vitamin A [45]).

#### *2.3. Lifestyle index score*

The lifestyle index score used in this study was generated according to public health and cancer prevention recommendations [46–48]. It was based on eleven factors: intake of red and processed meat, white meat, cream, cheese, fish, fruit and vegetables (excluding potatoes), physical activity, BMI, smoking, alcohol consumption, and breastfeeding, as described elsewhere [35].

For each participant, we calculated a HLI score based on eleven factors by assigning 0, 0.5 or 1 point to categories of each factor. As presented in Table 1, the healthy lifestyle behaviors were defined as limiting intake of red meat and avoiding processed meat (red and processed meat <500 g/week and processed meat intake <3 g/day), consuming more white meat (≥2 times per week), consuming more fish (≥2 times per week), high fruit and vegetable

consumption (at least 5 servings per day), no cream or cheese consumption, no alcohol consumption, never having smoked, having a high physical activity level (at least 60 minutes of moderate or 30 minutes of vigorous physical activity daily), a healthy BMI ( $<25 \text{ kg/m}^2$ ), and longer cumulative duration of breastfeeding ( $\geq 24$  months).

We assigned a lifestyle index score to participants by summing the individual scores for each of the lifestyle factors, consequently, the lifestyle index score ranged from 0 (least healthy) to 11 points (most healthy).

#### *2.4. Statistical analysis*

Descriptive statistics summarizing subject characteristics were calculated. Conditional and unconditional logistic regression models were used to estimate associations between HLI scores and risk of BC for all women combined and by menopausal status. HLI was modeled as a continuous (1-point increment) and categorical variable (tertiles). The HLI score was categorized into tertiles based on the score distribution of controls, with the lowest tertile (0 to 8.5 points) as the reference group. Multivariate adjusted odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were estimated, adjusting for age (continuous), number of live births (nulliparous, 1 to 3,  $\geq 4$ ), menopausal status combined with age at menopause (premenopausal, postmenopausal  $\leq 47$  years, and postmenopausal  $>47$  years), history of oral contraceptives (yes, no), family history of BC (yes/no), wealth score (continuous), age at first full-term pregnancy (nulliparous,  $<20$  years,  $\geq 20$  years) and energy intake (continuous), when appropriate. In stratified analyses by menopausal status, models were further adjusted for area of residence (urban/rural). None of other potential confounders listed in Table 2 changed our risk estimates by 10% or more. Because the association between BMI and BC risk differs by menopausal status, further analyses were conducted after excluding the BMI component from our HLI score. Sensitivity analyses were also performed with the exclusion of the cream and cheese components from the HLI score respectively. None of these sensitivity analyses materially altered our results (data not shown). Tests for trend were conducted by treating the HLI score as a continuous variable in the regression models. Median values in controls were used as cut-off points for age at menopause and number of live births. Due to the low frequency of postmenopausal hormone use, this variable was excluded from the analysis.

Data analysis was performed using SPSS, version 20 software. In all statistical analyses, p-values were two-sided and considered statistically significant if lower than 0.05.

#### *2.5. Ethical considerations*

The study protocol was approved by the Faculty of Medicine and Pharmacy of Casablanca Research Ethics Committee and the National Control Commission for the Protection of Personal Data (No.A-RS-192-2015).

### 3. Results

Individual components of the HLI scores and their distribution among cases and controls are presented in Table 1. Compared with controls, cases consumed more red and processed meat and cheese, and less white meat, fish, vegetables and fruits, and were less physically active and had lower levels of breastfeeding for at least 24 months. BMI was not significantly different between cases and controls.

The distribution of the selected characteristics of cases and controls are shown in Table 2. The mean age ( $\pm$ SD) of cases and controls were 49.7 ( $\pm$ 11.3) and 49.5 ( $\pm$ 11.5) years, respectively. Compared with controls, cases were more likely to be older at first full-term pregnancy and at age of menopause, and to have a lower number of live births, family history of BC, history of oral contraceptive use, lower wealth score and higher energy intake. The mean of the HLI score ( $\pm$ SD) in cases and controls was 8.1 ( $\pm$ 1.1) and 9.0 ( $\pm$ 0.9) respectively, ( $p < 0.01$ ).

Table 3 presents the multivariate-adjusted ORs and 95 % CIs between the HLI score and BC risk for all women, and by menopausal status. After adjustment for potential confounders, a higher HLI score was associated with a lower risk of BC, the adjusted OR comparing the highest to the lowest tertiles was 0.15 (95% CI: 0.07–0.32) for all women, 0.22 (95% CI: 0.10–0.49) for premenopausal women, and 0.11 (95% CI: 0.04–0.30) for postmenopausal women. Modeled as a continuous variable, one-point increment in the HLI score was associated with 56% (95% CI: 39–68%), 49% (95% CI: 30–63%), and 59% (95% CI: 40–72%) lower risk of BC in all, premenopausal, and postmenopausal women, respectively. After excluding the BMI component from the HLI score, the healthy lifestyle remained significantly associated with decreased risk of BC in all, premenopausal, and postmenopausal women.

### 4. Discussion

This case-control study is the first one in Morocco to evaluate the association between HLI (including healthy diet, high physical activity, low BMI, smoking, alcohol consumption, and longer duration of breastfeeding) and the risk of BC among Moroccan women. The results showed that a high HLI score was inversely associated with risk of BC, in pre- and postmenopausal women.

The findings of our study are in line with previously published studies in other populations that found inverse associations between BC risk and HLIs. Using the similar definition of our HLI score, a case-control study conducted by McKenzie et al. among Māori women in New Zealand, reported a 53% lower odds of BC for women in the top tertile of the HLI score compared to those in the bottom tertile (OR= 0.47, 95% CI: 0.23–0.94) [35]. Similarly, in the large Women's Health Initiative study, Arthur et al. found that women in the highest quintile level of the HLI score had a 30% reduced risk of BC (HR= 0.70, 95% CI: 0.64–0.76) compared to those in the lowest quintile of the index [37]. More recently, the Canadian Study of Diet found that an increase of a unit in the HLI score was associated with 3% reduction of BC risk among postmenopausal women (HR= 0.97, 95% CI: 0.94–0.99) [38].

In a Mexican case-control study where the HLI was defined as the combined effect of moderate and/or vigorous-intensity physical activity, low consumption of fat, processed foods, refined cereals, complex sugars, never having smoked (or <100 cigarettes) and never consuming alcohol, women in the highest quintile of the HLI had significantly lower odds of BC risk compared with women in the lowest quintile in both pre- (OR= 0.50, 95% CI: 0.29–0.84) and postmenopausal women (OR= 0.20, 95% CI: 0.11–0.37) [36]. The multinational European Prospective Investigation into Cancer and Nutrition (EPIC) cohort found 26% lower risk of BC among postmenopausal women when the fourth category of the lifestyle index (most healthy) was compared to the second (reference) category of the index score (HR = 0.74, 95% CI: 0.66–0.83) [34]. Their healthiest behaviors were defined as never smoking, no consumption of alcohol, high physical activity, low BMI and healthy diet (high in cereal fiber, fatty fish, folate, with a high ratio of polyunsaturated to saturated fat, high intake of fruits and vegetables and low in margarine/trans-fat and glycemic load). However, the French E3N cohort study, considered healthy index as having a BMI between 18.5 and 25 kg/m<sup>2</sup>, consuming at least 5 servings of vegetables and fruit per day, having a recreational physical activity of at least 20 MET-hour per week, being never smoker and drinking less than one alcoholic beverage per day [30], showed a statistically non-significant inverse association between HLI score and BC risk.

Our results are also consistent with the findings of prior studies that used a score based on adherence to the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) and/ or the American Cancer Society (ACS) recommendations [27,49–52]. For instance, an EPIC study reported that women within the highest category of the WCRF/AICR score had 16% lower risk for developing BC compared with those in the first category of the score (HR= 0.84, 95% CI: 0.78–0.90) [27]. Similarly, the Swedish Mammography Cohort showed that women who met six to seven recommendations of WCRF/AICR had a 51% decreased risk of BC compared to women meeting only zero to two recommendations (HR= 0.49, 95% CI: 0.35–0.70) [52]. The Canadian National Breast Screening Study reported that meeting the ACS guidelines was associated with 31% reduction of BC risk among Canadian women (HR= 0.69; 95% CI: 0.49–0.97) [49].

In this study, the models excluding BMI did not substantially change risk estimates, suggesting that BMI is not the main driver in our HLI score. Similarly, no major change in BC risk was observed in the VITamins And Lifestyle [53] and EPIC [27] cohort studies when BMI was excluded from the index scores. However, a significant reduction in BC risk was observed in the Cancer de Mâma study after excluding the BMI component [54]. An important advantage of our study is that weight and height were measured by interviewers and not self-reported.

In this study, the inverse association between healthy lifestyle and the breast cancer risk is intensified compared to that shown in other populations. This may be due to the existence of a bias in exposure assessment in our study. Given that the majority of breast cancer cases are diagnosed at late stages in Moroccan women [55], the effects of the disease or their symptoms

may have affected lifestyles of our cases (e.g. physical activity) toward a less healthy one before their diagnosis of breast cancer.

Our study has some limitations. Due to the retrospective nature of this study, most of the data were reported by participants and could be subject to recall bias. However, we recruited incident cases prior to any treatment and participants were not aware of potential risk factors for BC, and therefore measurement errors are most likely random (non-differential misclassification). Another limitation is the relatively small sample size particularly after stratification by menopausal status. This limitation restricted conducting finer stratification, and testing the contribution of each component of the index in risk reduction of BC. Future larger studies are needed in the Moroccan population.

In addition, considering that cases were significantly more likely to have a lower wealth score than controls, the possibility of selection bias cannot be ruled out in this study. However, this probable difference between cases and controls on socioeconomic level was shown in our previous study [56] on BC. It is therefore particularly important to investigate the relationship between the socioeconomic level and BC risk in the Moroccan context.

The limitation related to the construction of the index is detailed elsewhere [35]. For instance, the index includes foods for which the consumption could be interrelated. The index could also be imprecise for any vegetarians included in the study, because of the lack of information about alternative protein sources. In addition, the index components were equally weighted, without taking into account the unequal impact of each factor on cancer risk.

Additionally, due to the lack of dietary recommendations specific to the Moroccan population, our HLI score was based on international public health and cancer prevention recommendations. However, there is a clear need for developing dietary guidelines specific to the Moroccan population.

This study has several strengths. First, this is the first epidemiological study to investigate the association between HLI score and BC risk in Morocco and in North Africa. Second, the selection of population-based controls in our study may have improved the representation of the Fez population. Third, the adjustment for potential confounders, including socio-economic level assessed by a validated wealth score. Fourth, a high participation rate in both cases and controls.

In conclusion, the results showed that high HLI score may be associated with a decreased risk of BC in Moroccan women. These findings suggest that future breast cancer prevention efforts should focus on educating the Moroccan population about the benefits of healthy lifestyle including healthy diet, high physical activity, and breastfeeding. Future efforts should also address policies that will help institute interventions for breast cancer and chronic disease prevention.

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## **Competing interests**

There is no conflict of interest or competing financial interests.

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**Table 1.** Individual components of the healthy lifestyle index score and their distribution among cases and controls (N (%)).

Health recommendations & index component	Index points	Cases	Controls	<i>P</i> difference
		n (300)	n (300)	
<b>Limit intake of red meat and avoid processed meat</b>				
<b>Marker: Red meat and processed meat</b>				0.03
Red and processed meat $\geq$ 500 g/wk or processed meat intake $\geq$ 50 g/d	0	7 (2.3)	4 (1.3)	
Red and processed meat <500 g/wk and processed meat intake 3 to <50 g/d	0.5	26 (8.7)	12 (4.0)	
Red and processed meat <500 g/wk and processed meat intake <3 g/d	1	267 (89.0)	284 (94.7)	
<b>Choose a variety of protein foods</b>				
<b>Marker: White meat</b>				<0.001
<1 time per week	0	27 (9.0)	11 (3.7)	
1 time per week	0.5	69 (23.0)	53 (17.7)	
$\geq$ 2 times per week	1	204 (68.0)	236 (78.7)	
<b>Increase the amount and variety of seafood</b>				
<b>Marker: Fish</b>				<0.01
<1 time per week	0	63 (21.0)	27 (9.0)	
1 time per week	0.5	91 (30.3)	105 (35.0)	
$\geq$ 2 times per week	1	146 (48.7)	168 (56.0)	
<b>Limit the consumption of energy-dense foods</b>				
<b>Marker: Cream</b>				0.63
$\geq$ 2 times per week	0	18 (6.0)	13 (4.3)	
1 time per week	0.5	20 (6.7)	19 (6.3)	
<1 time per week	1	262 (87.3)	268 (89.3)	
<b>Reduce the intake of calories from solid fats</b>				
<b>Marker: Cheese</b>				<0.01
$\geq$ 2 times per week	0	76 (25.3)	64 (21.3)	
1 time per week	0.5	93 (31.0)	155 (51.7)	
<1 time per week	1	131 (43.7)	81 (27.0)	
<b>Eat mostly foods of plant origin</b>				
<b>Marker: Vegetables &amp; fruits</b>				<0.01
<200 g/d	0	43 (14.3)	19 (6.3)	
200 – 400 g/d	0.5	176 (58.7)	63 (21.0)	
$\geq$ 400 g/d	1	81 (27.0)	218 (72.7)	
<b>Be physically active as part of your everyday life</b>				
<b>Marker: Exercise <sup>a</sup></b>				<0.01
<30 min of moderate exercise or <15 min of vigorous exercise per day.	0	65 (21.7)	25 (8.3)	
30 to <60 min of moderate exercise or 15 to <30 min of vigorous exercise per day.	0.5	66 (22.0)	21 (7.0)	
$\geq$ 60 min of moderate exercise or $\geq$ 30 min of vigorous exercise per day.	1	169 (56.3)	254 (84.7)	
<b>Be as lean as possible without becoming underweight</b>				
<b>Marker: BMI</b>				0.19

≥30 kg/m <sup>2</sup>	0	118 (39.3)	97 (32.3)	
25 – 29 kg/m <sup>2</sup>	0.5	113 (37.7)	123 (41.0)	
<25 kg/m <sup>2</sup>	1	69 (23.0)	80 (26.7)	
<b>Limit alcoholic drinks</b>				
<b>Marker: Alcohol</b>				0.19
≥10 g/day	0	3 (1.0)	0 (0.0)	
<10 g/day	0.5	3 (1.0)	2 (0.7)	
Never	1	294 (98.0)	298 (99.3)	
<b>Do not smoke</b>				
<b>Marker: Smoking</b>				0.01
Current	0	7 (2.3)	0 (0.0)	
Former	0.5	6 (2.0)	2 (0.7)	
Never	1	287 (95.7)	298 (99.3)	
<b>Breastfeed infants for at least 24 months<sup>b</sup></b>				
<b>Marker: Breastfeeding<sup>c</sup></b>				<0.01
Never breastfeed	0	76 (25.3)	27 (9.0)	
>0 – <24 months	0.5	53 (17.7)	34 (11.3)	
≥24 months	1	171 (57.0)	239 (79.7)	

<sup>a</sup> Physical activities (including occupational, recreational and household activities).

<sup>b</sup> Based on Moroccan public health recommendations (<http://www.sante.gov.ma>).

<sup>c</sup> Cumulative breastfeeding.

**Table 2.** Selected characteristics of cases and controls (numbers and percentages; mean values and standard deviations).

Characteristics	Cases	Controls	<i>P</i> <i>difference</i>
	(n = 300)	(n = 300)	
<b>Area of residence</b>			0.53 (Matched)
Urban	204 (68.0)	204 (68.0)	
Rural	96 (32.0)	96 (32.0)	
<b>Marital status</b>			<b>&lt;0.01</b>
Single	37 (12.3)	13 (4.3)	
Married	196 (65.3)	238 (79.3)	
Divorced	27 (9.0)	7 (2.3)	
Widowed	40 (13.3)	42 (14.0)	
<b>Educational level</b>			0.47
Illiterate	200 (66.7)	200 (66.7)	
Elementary /Koranic school	51 (17.0)	54 (18.0)	
Secondary school	37 (12.3)	28 (9.3)	
High school /Technical or professional school	12 (4.0)	18 (6.0)	
<b>Menopausal status</b>			0.23
Premenopausal	161 (53.7)	151 (50.3)	
Postmenopausal	139 (46.3)	149 (49.7)	
<b>Age at menopause<sup>a</sup> (year)</b>			<b>&lt;0.01</b>
≤47	51 (36.7)	108 (72.5)	
>47	81 (58.3)	27 (18.1)	
Missing	7 (5.0)	14 (9.4)	
<b>Number of live births</b>			<b>&lt;0.01</b>
Nulliparous	69 (23.0)	21 (7.0)	
1 to 3	119 (39.7)	130 (43.3)	
≥4	112 (37.3)	149 (49.7)	
<b>History of oral contraceptive</b>			<b>&lt;0.01</b>
Yes	182 (60.7)	107 (35.7)	
No	118 (39.3)	193 (64.3)	
<b>Family history of breast cancer<sup>b</sup></b>			<b>&lt;0.01</b>
Yes	28 (9.3)	12 (4.0)	
No	272 (90.7)	288 (96.0)	
<b>Age at entry (year)</b>	49.7 ± 11.3	49.5 (±11.5)	0.85 (Matched)
<b>Age at menarche (year)</b>	13.5 ± 1.7	13.7 ± 1.2	0.07
<b>Wealth score<sup>c</sup></b>	5.9 ± 1.7	7.6 ± 1.6	<b>&lt;0.01</b>
<b>Age at first full-term pregnancy<sup>d</sup> (year)</b>	22.9 ± 6.1	20.7 ± 5.1	<b>&lt;0.01</b>
<b>Energy intake (kcal/d)</b>	3034.8 ± 745.5	2907.9 ± 690.2	<b>0.03</b>
<b>Lifestyle index score</b>	8.1 ± 1.1	9.1 ± 1.0	<b>&lt;0.01</b>

<sup>a</sup> Among postmenopausal women.

<sup>b</sup> First- and second-degree relatives.

<sup>c</sup> based on household assets including electricity, television, cell phone, refrigerator, indoor bath or shower, indoor tap, flush toilet, washing machine, car and landline phone.

<sup>d</sup> Among parous women.

**Table 3.** Multivariate-adjusted odds ratios and 95 % confidence intervals of breast cancer associated to the healthy lifestyle index score, overall and by menopausal status.

	Overall (300/300)		Premenopausal (161/151)		Postmenopausal (139/149)	
	Ca /Co	OR <sup>a</sup> (95% CI)	Ca /Co	OR <sup>b</sup> (95% CI)	Ca /Co	OR <sup>c</sup> (95% CI)
<b>Healthy lifestyle index (rang=1-11)</b>						
Tertile 1 (lower)	155/55	Reference	78/28	Reference	77/27	Reference
Tertile 2 (medium)	95/100	0.36 (0.18-0.73)	57/50	0.66 (0.32-1.34)	38/50	0.21 (0.09-0.50)
Tertile 3 (upper)	50/145	0.15 (0.07-0.32)	26/73	0.22 (0.10-0.49)	24/72	0.11 (0.04-0.30)
P trend		<0.01		<0.01		<0.01
1-point increase of score		0.44 (0.32-0.61)		0.51 (0.37-0.70)		0.41 (0.28-0.60)
P-value		<0.01		<0.01		<0.01
<b>Healthy lifestyle index excluding BMI component (rang=1-10)</b>						
Tertile 1 (lower)	152/47	Reference	82/26	Reference	70/21	Reference
Tertile 2 (medium)	92/116	0.30 (0.15-0.59)	54/58	0.52 (0.25-1.08)	38/58	0.16 (0.06-0.40)
Tertile 3 (upper)	56/137	0.15 (0.06-0.33)	25/67	0.22 (0.09-0.51)	31/70	0.12 (0.04-0.32)
P trend		<0.01		<0.01		<0.01
1-point increase of score		0.39 (0.28-0.55)		0.47 (0.33-0.67)		0.41 (0.28-0.61)
P-value		<0.01		<0.01		<0.01

<sup>a</sup> Odds ratios estimated by conditional logistic regression and adjusted for age (continuous), number of live births (nulliparous, 1 to 3, ≥4), menopausal status and age at menopause combined (premenopausal, ≤47 years, >47 years, missing), history of oral contraceptive (yes, no), family history of breast cancer (yes/no), wealth score (continuous), age at first full-term pregnancy (nulliparous, <20 years, ≥20 years) and energy intake (continuous).

<sup>b</sup> Odds ratios estimated by unconditional logistic regression and adjusted for age (continuous), area of residence (urban/rural), number of live births (nulliparous, 1 to 3, ≥4), history of oral contraceptive (yes, no), family history of breast cancer (yes/no), wealth score (continuous), age at first full-term pregnancy (nulliparous, <20 years, ≥20 years) and energy intake (continuous).

<sup>c</sup> Odds ratios estimated by unconditional logistic regression and adjusted for age (continuous), area of residence (urban/rural), age at menopause (≤47 years, >47 years, missing), number of live births (nulliparous, 1 to 3, ≥4), history of oral contraceptive (yes, no), family history of breast cancer (yes/no), wealth score (continuous), age at first full-term pregnancy (nulliparous, <20 years, ≥20 years) and energy intake (continuous).

## **4. Facteurs anthropométriques et risque de cancer du sein chez les femmes de la région de Fès, Maroc**

### **4.1. Introduction**

Plusieurs études épidémiologiques et méta-analyses ont permis de mettre en évidence des associations entre les mesures anthropométriques et le risque de cancer du sein [54,125–129]. L'IMC est inversement associé au risque de cancer du sein avant la ménopause, mais positivement associé à ce risque en période post-ménopausique [54,127,128]. Une taille élevée à l'âge adulte est largement associée à une augmentation du risque de cancer du sein pré et post-ménopausique [54]. Certaines études rapportent qu'un tour de taille, considéré comme bon indicateur de l'obésité abdominale, est positivement associé au risque de cancer du sein avant et après la ménopause [129]. Similairement, un gain de poids au cours de la vie adulte est associé à une augmentation probable du risque de cancer du sein post-ménopausique chez les femmes n'ayant jamais utilisé de traitement hormonal substitutif [130,131]. En revanche, un IMC élevé à l'enfance ou l'adolescence est inversement associé au risque de cancer du sein avant et après la ménopause [132,133].

Au Maroc, comme dans de nombreux pays en transition épidémiologique et nutritionnelle, la prévalence de l'obésité et du surpoids ne cessent de croître. Selon les données du Haut-Commissariat au Plan- Maroc [1], la prévalence du surpoids et de l'obésité chez les femmes Marocaines est passée respectivement de 29,9% et 16,0% à 34,7% et 26,8% entre 2001 et 2011. En outre, selon les estimations du GCO du CIRC, la fraction de cancer du sein postménopausique attribuable à un excès d'IMC chez les femmes marocaines est estimée à 11,2% en 2012 [13].

Par ailleurs, peu d'études épidémiologiques sont disponibles sur l'association entre les mesures anthropométriques et le risque de cancer du sein chez les femmes d'Afrique du Nord.

L'objectif de ce travail était d'étudier les associations entre les différents indicateurs anthropométriques, l'évolution de la trajectoire de la silhouette et le risque de cancer du sein chez les femmes Marocaines en pré- et post-ménopause dans la région de Fès.

### **4.2. Méthodes**

Les analyses de cette étude étaient réalisées à partir des données collectées dans le cadre de l'étude "BreCaFez Study".

Les mesures anthropométriques (poids, taille, tour de taille/tour de hanches...) ont été recueillies selon les recommandations de Lohman et al. [134], par des enquêteurs formés à cet effet. L'échelle largement validée de Sørensen [81] a été utilisée pour évaluer la forme de la silhouette à différents âges. Les femmes étaient invitées à choisir parmi neuf figures de silhouette féminine, allant de la plus faible (nombre = 1) à la plus forte (nombre = 9), celle qui se rapprochait le plus de leur silhouette à l'enfance (6-11 ans), l'adolescence (12-18 ans) et l'âge de 19 à 25 ans.

Nous avons réalisé des analyses de trajectoires de l'évolution de la silhouette à travers l'âge en utilisant l'approche développée par Jones B et Nagin DS [135] (the SAS Proc Traj (<http://www.andrew.cmu.edu/user/bjones/index.htm>)), qui permet de distinguer des sous-

groupes de femmes ayant une trajectoire d'évolution de la silhouette similaire au cours du temps.

Les odds ratios (OR) et leurs intervalles de confiance à 95% ont été estimés à partir de régressions logistiques non conditionnelles, en ajustant sur les variables de confusion.

Toutes les analyses ont été effectuées séparément chez les femmes en pré- et en post-ménopause.

### **4.3. Principaux résultats**

Un tour de taille élevé était associé à un risque élevé de cancer du sein chez les femmes en préménopause (Tertile 3 versus Tertile 1 : OR = 2,92, IC 95%: 1,33–6,42; p tendance <0,01) et en postménopause (Tertile 3 versus Tertile 1 : OR = 4,46, IC 95%: 1,86–10,66; p tendance <0,01). Similairement, un tour de hanches élevé était associé à un risque élevé de cancer du sein chez les femmes en préménopause (Tertile 3 versus Tertile 1 : OR = 3,00, IC 95%: 1,42–6,33; p tendance = 0,01) et en postménopause (Tertile 3 versus Tertile 1 : OR = 4,08, IC 95%: 1,76–9,42; p tendance <0,01). En revanche, une large silhouette à l'enfance (6–11 ans) était associée à une diminution significative de risque de cancer du sein chez les femmes en préménopause (large silhouette versus faible silhouette : OR = 0,31, IC 95%: 0,12–0,80; p tendance = 0,01) et à la limite de la signification statistique chez les femmes en postménopause (large silhouette versus faible silhouette : OR = 0,40, IC 95%: 0,15–1,07; p tendance = 0,05). L'analyse des trajectoires montrent que le risque de cancer du sein était augmenté chez les femmes ayant une forte évolution de trajectoire de la silhouette, comparées aux femmes ayant une faible évolution (Préménopause : OR = 2,74, IC 95%: 1,03–7,26 ; Postménopause : OR = 3,56, IC 95%: 1,34–9,44).

Par ailleurs, l'IMC actuelle, l'IMC à 20 ans et la prise de poids à partir de 20 ans n'étaient pas associés au risque de cancer du sein chez les femmes dans cette étude.

### **4.4. Forces et faiblesses de l'étude**

Cette étude présente certaines limites. Premièrement, la taille de notre population d'étude est relativement faible en particulier après stratification sur le statut ménopausique, et la puissance statistique était donc probablement insuffisante pour détecter certaines associations faibles. Deuxièmement, les données sur la silhouette et le poids dans le passé étaient basés sur une auto-déclaration, ce qui pouvait entraîner des erreurs de mémoire et de déclaration. Néanmoins, nous pensons que ces erreurs peuvent entraîner un biais de classement non différentiel. Troisièmement, nous n'avons pas de données sur les sous-types moléculaires de cancer du sein. Quatrièmement, comme déjà évoqué, le diagnostic de cancer du sein se fait tardivement pour un grand nombre de cas au Maroc, toutefois, nous ne pouvons pas exclure l'effet de la maladie sur certaines mesures anthropométriques avant le diagnostic du cancer du sein chez certains cas de notre étude.

En plus des forces liées globalement à notre étude citées précédemment dans la partie 4 du Chapitre III, il est important de souligner que cette étude est la première au Maroc qui explore l'association entre différentes mesures anthropométriques, l'évolution de trajectoire de la silhouette et le risque de cancer du sein chez les femmes Marocaines.



#### **4.5. Conclusion**

Cette étude suggère l'existence de certaines associations entre les facteurs anthropométriques et le risque cancer du sein chez les femmes Marocaines. Elle montre qu'un excès d'adiposité abdominale est associé à une augmentation de risque du cancer de sein. Par contre, elle suggère que la silhouette à l'enfance est inversement associée à ce risque chez les femmes de notre population. Elle suggère également qu'une forte évolution de trajectoire de la silhouette (entre 6 et 25 ans) est associée à un risque accru de cancer du sein. Ces conclusions doivent être confirmées par des études prospectives de plus grande puissance tenant compte les sous-types moléculaires de cancer du sein.

#### **4.6. Article 4**

##### **Body Size, Silhouette Trajectory and the Risk of Breast Cancer in a Moroccan Case-control Study.**

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## **Abstract**

### **Introduction**

There is convincing evidence demonstrating that body size is strongly associated with breast cancer in westernized countries, though little is known regarding these associations in countries undergoing nutrition transitions like for North African countries. The aim of this study was to explore the association between various body size characteristics, silhouette trajectory and the risk of breast cancer risk among Moroccan women.

### **Methods**

In this case–control study conducted in Fez region- Morocco (2016–2017), detailed measures of body size were collected for 300 cases of histopathologically–confirmed breast cancer and 300 healthy controls. Unconditional logistic regression was used to assess the association between body sizes and breast cancer risk adjusting for confounding factors.

### **Results**

High waist circumference (WC) and hip circumference (HC) were associated with increased breast cancer risk in pre- and post-menopausal women ( $p$  trend  $<0.01$  for both WC and HC). Body shape at young ages (6-11 years) was inversely associated with risk of breast cancer in premenopausal ( $p$  trend= 0.01) and postmenopausal women ( $p$  trend= 0.05). Women with the greatest increase in body shape trajectory had higher risk for both pre- and post-menopausal breast cancer (T3 vs. T1 trajectory: OR= 2.74 (1.03–7.26), and OR= 3.56 (1.34–9.44), respectively).

### **Conclusion**

Our findings suggest that central adiposity, body shape at young ages, and silhouette trajectory may play a role in the development of pre- and postmenopausal breast cancer among Moroccan women. Larger prospective studies are needed to confirm our findings and to explore these associations with breast cancer subtypes.

**Keywords** Breast cancer; body size; Anthropometry; Adiposity; Morocco

## **Introduction**

Breast cancer (BC) is the most commonly diagnosed cancer and a leading cause of cancer death among women worldwide [1] and increasing rapidly in low/middle income countries undergoing societal and nutritional transitions like Morocco [2]. In 2018, this disease is accounting for 36.9% of all new cancer cases among Moroccan women, and is estimated to be responsible for 24.7% of cancer mortality in Moroccan women [2].

Some modifiable risk factors for BC have already been identified, including body size [3]. A larger adult body size estimated by body mass index (BMI) has been shown to be positively associated with postmenopausal BC risk [4,5], but inversely associated with premenopausal BC risk [4,6]. Adult-attained height [4] and central obesity estimated by waist circumference (WC) have been linked to an increased BC risk for both pre- and post-menopausal women [7]. It has been also reported that weight gain in adulthood is probably associated with increased risk of postmenopausal BC among women who have never used hormone replacement therapy (HRT) [8,9]. Also, some evidence suggest that larger body size in early life is associated with decreased risk of BC diagnosed at premenopausal and postmenopausal ages independently of adult BMI [10,11].

Increased excess body weight and obesity among women are increasingly a public health concern in many countries undergoing epidemiologic and nutritional transitions, including Morocco. According to the last report of the High Commission for Planning of Morocco, the prevalence of overweight and obesity among Moroccan women increased respectively from 29.9% and 16.0% in 2001 to 34.7% and 26.8% in 2011 [12]. Moreover, according to the Global Cancer Observatory (GCO)- 2018 of the International Agency for Research on Cancer, the fraction of postmenopausal BC attributable to excess of BMI among Moroccan women is estimated to 11.2% in 2012 [2]. However, the role of anthropometric factors in the development of BC has not been fully explored in an epidemiological context in Morocco.

Briefly, the relationship between body size and BC risk has been evaluated mainly in Western countries, and little is known about risk factors among women in developing countries. Therefore, this study aims to investigate the association between diverse measures of body size, silhouette trajectory and the risk of pre- and post-menopausal BC among Moroccan women.

## **Methods**

### ***Study Population***

The BreCaFez Study is a case–control study conducted in the Fez region- Morocco, between February 2016 and August 2017. A total of 300 incident BC cases and 300 controls were recruited in the study. The design of the study has been described in detail elsewhere [13]. Briefly, cases were recruited from the Medical Oncology Center of the University Hospital in Fez, which is a referral center for BC for outpatient health centers in the region. The cases were newly-diagnosed histologically-confirmed in situ or invasive BC and had not received any treatment. Controls were randomly selected among women with no previous history of

cancer, visiting one of six outpatient primary health centers (three urban and three rural) in the Fez region. Control subjects were matched individually to the cases by age [ $\pm 5$  years (72% of pairs matched by age  $\pm 1$  year)] and area of residence (urban vs. rural). Women who accompanied patients with any type of cancer were ineligible for recruitment as controls. Further eligibility criteria for cases and controls were that the participants were not pregnant or nursing, and were able to give informed consent.

The response rates among eligible women were 96.7% for cases and 87.9% for controls.

### ***Data collection***

Participants were interviewed at enrolment in the study by four interviewers who were trained in conducting interviews in a standardized way. Data were collected using an in depth questionnaire to collect information about sociodemographic characteristics, occupational history, anthropometric measurements, family history of cancer including BC, menstrual and reproductive history (e.g., age at menarche, age at first full-term pregnancy, parity, menopausal status, age at menopause, history of breastfeeding), hormone use, smoking, alcohol consumption, physical activity and dietary habits.

Socio-economic status was assessed using a validated wealth score based on household assets owned by participants including electricity, refrigerator, television, washing machine, cell phone, indoor bath or shower, indoor tap, flush toilet, car and landline phone [14]. The questionnaire also assessed physical activity of women in the last 12 months, as described in detail elsewhere [13]. In this study, we quantified the intensity of physical activity using a MET-hours per week of all activities combined, including occupational, recreational and household activities. Total MET-hours per week for each category of activity were calculated by multiplying the number of hours per week spent by the MET score corresponding to that category. A Food Frequency Questionnaire previously validated for the Moroccan population was used to assess dietary intake during the previous 12 months. Postmenopausal status was defined as self-reported absence of menstruation in the last 12 months.

### ***Body size variables***

Anthropometric measurements were obtained at recruitment by trained interviewers according to the recommendations of Lohman et al. [15]. Weight (with light clothing) and standing height (without shoes) were measured using standard equipment. Weight was measured to the nearest 0.5 kg and height was measured to the nearest 0.5 cm. Current BMI was calculated as weight in kilograms divided by height in squared meters. Current BMI was classified according to the World Health Organization classification, as normal weight ( $< 25$  kg/m<sup>2</sup>), overweight (25–29 kg/m<sup>2</sup>), or obese ( $\geq 30$  kg/m<sup>2</sup>). Underweight women with BMI  $< 18.5$  kg/m<sup>2</sup> (1 case, 1 control) were grouped with normal weight women. Young-adult BMI was based on measured height at interview and recalled weight at 20 years, which has been previously validated in other studies [16]. Weight gain since the age of 20 years was calculated as the difference between current weight and recalled weight at age 20 years and women who lost weight were excluded (11 cases, 7 controls). WC was measured at the natural indentation of the waist and hip circumference (HC) at the greatest protrusion of the buttocks. WC and HC

were measured with light clothing. The waist-to-hip ratio (WHR) was calculated as WC in centimeters divided by HC in centimeters.

Information on body shape at different ages was collected by the commonly used Stunkard's figure rating scale [17]. Women were asked to select among nine female silhouette drawings, ranging from very thin (number = 1) to very fat (number = 9), which best described their body shape at different periods of life: childhood (6-11 years), adolescence (12-18 years), and young adult (19-25 years). These body image pictograms were tested for validity and reliability in different settings, and have proven to be valid and reliable [18]. Because of the small numbers of women in some categories (as shown in Figure 1), the nine silhouettes were regrouped a priori (prior to analysis) as follows: for childhood: lean = figure 1, medium = figure 2, and large= figures 3 to 9; For adolescence: lean = figure 1–2, medium = figure 3, and large= figures 4 to 9.

### ***Statistical analyses***

All statistical analyses were done separately for pre- and post-menopausal women. The distributions of sociodemographic, reproductive, anthropometric and lifestyle characteristics were described as frequencies for categorical variables and means  $\pm$  standard deviations (SD) for continuous variables. Unconditional logistic regression was used to estimate the associations between various body size measurements and the risk of BC. Multivariate adjusted odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were estimated, adjusting for age (continuous), area of residence (urban/rural), wealth score (continuous), number of live births (nulliparous, 1 to 3,  $\geq 4$ ), history of oral contraceptives (yes, no), history of breastfeeding (yes, no), age at first full-term pregnancy (nulliparous,  $< 20$  years,  $\geq 20$  years) and physical activity (continuous) (based on 10% change in the OR). Additional sensitivity analyses adjusting for current BMI were also performed. Except for current BMI where the WHO categories were used, the body size variables were categorized according to the tertile distribution among controls, separately in pre- and post-menopausal women. Test for trend was performed by using tertiles scores as continuous variables in the models.

Group based trajectory modelling was used to estimate the different groups of body shape evolution throughout life (trajectory) [19], based on nine reported silhouettes at childhood, adolescence, and aged young adult. This method is based on application of finite mixture modeling that define clusters of women having similar body shape evolution over time. The censored normal model of the SAS Proc Traj was used to carried out our silhouette analyses. Three distinct trajectories were estimated: T1, T2, and T3 (Figure 2). Selection of the number of trajectories (groups) was based on the Bayesian information criterion and the proportion of women included in each group [19,20]. Women with missing information on body shape were excluded from analyses.

In this study, due to the very low frequency of postmenopausal hormone use, this variable was excluded from the analysis. Data analysis was performed using SPSS (version 20) and SAS (version 9.3). In all statistical analyses, p-values were two-sided and considered statistically significant if lower than 0.05.

## ***Ethical considerations***

All study participants provided written informed consent to participate in the study. The protocol of the study was approved by the Faculty of Medicine and Pharmacy of Casablanca Research Ethics Committee and the National Control Commission for the Protection of Personal Data (No.A-RS-192-2015).

## **Results**

### **Study population characteristics**

Characteristics of the study population, stratified by menopausal status, are shown in Table 1. The mean age ( $\pm$ SD) of cases and controls was 49.7 ( $\pm$ 11.3) and 49.5 ( $\pm$ 11.5) years, respectively. Among cases, about 53.7% were premenopausal and 46.3% were postmenopausal. Among controls, about 50.3% were premenopausal and 49.7% were postmenopausal.

Compared with controls, both premenopausal and postmenopausal BC cases were more likely to be older at first full-term pregnancy, and to have a lower number of live births, a history of oral contraceptive use, a lower wealth score, a higher WHR, WC and HC and are less likely to have a history of breastfeeding and to be physically active. Postmenopausal cases were more likely than controls to have an older age at menopause and to have a higher weight and BMI. Cases and control subjects did not show statistically significant differences in educational level and age at menarche.

Distribution of the study population by reported silhouettes for different ages are shown in Figure 1. The silhouette 2 was the most frequently drawing selected (50.0%) by women to describe their body shape for childhood, the silhouette 3 for adolescence (39.2%), and the silhouette 4 for young adulthood (29.6%).

Figure 2 presents the evolution of estimated trajectories of body size by age. Overall, three distinct trajectories were estimated, with at least 23.1% of the population in each category. The first trajectory "T1: low increase" showed a limited change of body shape over time, women in this group started with a low body shape at childhood and then slightly increased with age. This group of women represented 30.7% of the study population. The second trajectory "T2: Moderate increase" characterized by a moderate increase of body shape over the age periods, this group constituted 46.1% of the study population. The third trajectory "T3: Strong increase" showed a strong increase in body shape over time. The proportion of women with this trajectory was 23.1%.

### **Anthropometric measurements and BC risk**

The association between anthropometric measurements and BC risk stratified by menopausal status are shown in Table 2. Current BMI, height, weight and WHR were not significantly associated with BC risk in either pre- or post-menopausal women. High WC was associated with an increased risk of pre- and post-menopausal BC, the multivariate-adjusted ORs comparing the highest to the lowest tertile of WC were 2.92 (95% CI: 1.33–6.42) and 4.46 (95% CI: 1.86–10.66), respectively. Similarly, high HC was positively associated with risk of BC in both pre- and post-menopausal women (highest vs. lowest tertile: pre-menopausal: OR= 3.00,

95% CI: 1.42–6.33; post-menopausal 4.08, 95% CI: 1.76–9.42). For both WC and HC, further adjustment for current BMI did not significantly change the results. Neither young-adult BMI nor weight gain since the age of 20 years was associated with BC risk in the current study.

#### Body silhouettes, trajectories and BC risk

Table 3 shows the association between early-life reported silhouette and the risk of BC. A significant inverse association was observed between silhouette at childhood and BC risk for premenopausal women (large vs. lean silhouette: OR= 0.31, 95% CI: 0.12–0.80, p trend = 0.01), and a borderline significant inverse association for postmenopausal women (large vs. lean silhouette: OR= 0.40, 95% CI: 0.15–1.07, p trend = 0.05). Silhouette at 12-18 years was not associated with BC risk in our study.

The association between trajectories of body size (assessed via body silhouettes) and BC risk are shown in Table 4. Women with the greatest increase in body shape trajectory had higher risk of pre- and post-menopausal BC (T3 vs. T1 trajectory: OR= 2.74, 95% CI: 1.03–7.26, and OR= 3.56, 95% CI: 1.34–9.44, respectively).

#### **Discussion**

In this case-control study, we examined the association between various anthropometric characteristics, body shape trajectories and the risk of BC among Moroccan women in the Fez region. We found a statistically significant increase in pre- and post-menopausal BC risk among women with higher waist and hip circumferences. We also found an inverse association between body shape at young ages and BC risk. Additionally, our results suggest that women with greater increases in body shape trajectory had a higher risk of BC.

In this study, we did not observe any clear association between current BMI and the risk of BC. Previous studies have shown that higher BMI is associated with a decreased risk of BC among premenopausal women [4–6,21]. A recent pooled analysis from prospective studies from high income countries, including 758 592 premenopausal women, found a strong inverse association of BC risk with BMI at 18 through 54 years of age [6]. However, a meta-analysis from 31 prospective cohorts [22] and a meta-analysis from 50 prospective cohort and case-control studies [23], reported no association between BMI and premenopausal BC. Regarding findings from premenopausal African women, one case-control study from Nigerian women observed an inverse association between BMI and the risk of premenopausal BC [24], whereas, a case-control study from Tanzanian women reported no association [25]. Globally, it seems that studies conducted in high income countries reported a consistent inverse association between BMI and pre-menopausal BC, whereas studies are scarce in low-to-middle income countries. For postmenopausal BC, consistent evidence from the literature supported by the recent updated report of the World Cancer Research Fund (WCRF) & American Institute for Cancer Research (AICR) indicated a significant association between high BMI and increased risk of postmenopausal BC [4,5,21]. A dose-response meta-analysis including 31 prospective studies showed a 12% increased risk of postmenopausal BC for each 5 kg/m<sup>2</sup> increase in BMI [5]. Similarly, a more recent meta-analysis reported a positive non-linear association between BMI and the risk of postmenopausal BC, the Risk Ratio (RR) was 1.03 (95% CI: 1.02 – 1.05) per 1 kg/m<sup>2</sup> increase in BMI [22]. However, a recent study suggests

that women with normal BMI and excess body fat might have an increased risk for BC specifically after menopause [26]. This study concluded that normal BMI may be an inadequate proxy for predicting a risk of BC in postmenopausal women [26].

Although several mechanisms have been hypothesized, the pathophysiology underlying the association between BMI and BC is complex and remains unclear [22,27]. The increased risk in overweight and obese postmenopausal women may be explained by the higher level of estrogen produced by aromatase conversion in adipose tissue after the menopause [27,28], other mechanisms including altered levels of adipokines (leptin and adiponectin) and disrupted insulin/IGF signaling are also suggested to contribute to this link [27]. However, premenopausal obese women are more likely to have longer menstrual anovulatory cycles that reduce exposure of breast cells to estrogen, possibly resulting in decreased risk of BC in these women [29].

With regard to height and risk of BC, there is a large body of literature indicating that greater adult height is associated with higher risk of BC in both pre- and post-menopausal women [4,30]. Findings from the Million Women Study reported an increase of BC risk by 17% for every 10 cm increase in adult height [30]. On the other hand, some epidemiological studies including the current analysis, did not observe an association between height and the risk of BC [31,32]. Adult-attained height is determined by genetic factors, but also by some non-genetic factors such as environmental factors and childhood growth conditions including nutrition and diseases [33]. Circulating levels of insulin-like growth factor 1 (IGF1) in adulthood and childhood are positively correlated with adult height in women, and higher IGF-1 was consistently associated with an increased risk of BC [34].

While WHR is widely used as a measure of central obesity, some recent studies suggest that WC, which is highly correlated with visceral fat, might be a better indicator of BC risk than WHR [35]. Visceral fat can release inflammatory markers, adipokines and insulin-like growth factors (IGF) which may promote BC development [7,36]. In agreement with a recent meta-analysis of prospective studies [7], we found that central obesity measured by WC, but not by WHR, was associated with a higher risk of developing BC in pre- and post-menopausal women. Our findings were also in line with a study in African women (Nigeria) reported that higher waist circumference was associated with an increase of the risk of both pre- and post-menopausal BC (OR=2.40, 95% CI: 1.52–3.78; OR=2.21, 95% CI: 1.25–3.91, respectively) [37]. However, other studies reported an increased risk for post- but not pre-menopausal BC [38,39]. The associations between central adiposity and BC risk observed in this study are modestly stronger than what is shown in other studies. This could be attributed to bias arising during measurements in this study. It is noteworthy that waist and hip circumference were often measured with light clothing, potentially leading to differential bias in WC and HC measurements among overweight versus normal weight women.

BMI in early adulthood (e.g. at age 20 years) is inversely associated with risk of premenopausal BC [40,41], but this association may differ according to subtypes of BC defined by molecular status [40,42]. The AMBER Consortium Study reported that BMI at age 18 years was inversely associated with risk of ER+ BC, but not with ER- or triple negative BC [42]. However, results of this association among postmenopausal women are inconsistent [41,43]. As reported in some



studies [44], our results did not show any significant association between early adulthood body size and BC risk. However further studies exploring this association by molecular status of tumors in Moroccan women are needed.

Our results are in line with previous evidence indicating that adult weight gain (i.e. weight gain since age 20 years) is not related with premenopausal BC [9,40,45,46]. However, weight gain during adulthood has been reported in many studies to be associated with an increased risk of postmenopausal BC [8,9,40,45,46]. A recent meta-analysis reported a RR of 1.11 (95% CI: 1.09 to 1.13) for each 5 kg increase in adult weight gain for postmenopausal BC among women not using of HRT [8]. The lack of an association between adult weight gain and postmenopausal BC risk in our study may be due to error in the recalled weight at 20 years by elderly postmenopausal woman. Moreover, there is some evidence suggesting that the timing of weight gain, body fat distribution, and receptor status of the tumour may affect the association between adult weight gain and postmenopausal BC risk [8,45,46]. Globally, longitudinal investigations with measured anthropometric data are needed to clarify the association between body size throughout the life course and BC risk among Moroccan women.

Consistent with similar studies that used recalled body shape (Stunkard's scale) at different ages [10,11], we observed a decreased risk of BC among women with large body shape at young ages (6-11 years). The mechanisms behind the inverse association between body shape in early life and BC risk are not well understood [10,11,40,47]. It has been hypothesized that childhood adiposity may influence growth and maturation [40], and it is suggested to be associated with a slower pubertal growth which decreases the risk of BC [10,48]. Other suggested mechanisms involve endogenous hormone levels and breast density [40,47].

Few studies have assessed body shape trajectories and BC risk. Our findings showed that women with significant increases in body size had a higher BC risk than women with a slight increase or stable body size. The positive relationship between body shape trajectory and BC risk has also been reported in the CAMA study for pre- and post-menopausal women [49] and in the Nurses' Health Study for postmenopausal women [50].

Some limitations of the current study should be noted. First, our stratified analyses were limited by low statistical power, due to the relatively small sample size. Consequently, the statistical power might be insufficient to detect weak associations. Second, due to the case-control study design, body shape (silhouette) and weight in the past were based on self-report, which could result in misreporting errors due to inaccurate recall. However, such error would likely lead to a non-differential misclassification. Lastly, it has been shown that Moroccan women with BC have a higher likelihood of being diagnosed at advanced stages of the disease [51]; thus, we cannot exclude the possibility that certain current body size of our cases may have been affected by the disease, or its symptoms, prior to BC diagnosis.

This study also has several important strengths. To our knowledge, our study is the first to explore the association between body size, silhouette trajectory and the risk of BC in Moroccan women. Furthermore, we adjusted for a large battery of potential confounders in

our analyses. Moreover, high participation rates in both cases and controls may minimize selection bias.

In conclusion, we found that central adiposity estimated by WC was positively associated with both pre- and post-menopausal BC risk. Furthermore, we confirmed a previously reported inverse association between body shape at young ages and BC risk in pre- and post-menopausal women. We also found that trajectory reflecting large increase in body shape was associated with a higher risk of BC. Overall, these results are consistent with the literature (mainly derived from westernized countries). However, further longitudinal studies with larger sample size and receptors status of tumors could provide a more comprehensive insight into the association between body size and BC risk in Moroccan women.

### **Conflict of interest**

The authors declare that they have no competing interests.

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**Table 1: Characteristics of the cases and controls according to menopausal status in the BreCaFes Study (number (%) or mean  $\pm$  standard deviation).**

Characteristics	Premenopausal women			Postmenopausal women		
	Cases (n = 161)	Controls (n = 151)	<i>P</i> value	Cases (n = 139)	Controls (n = 149)	<i>P</i> value
<b>Age at entry</b> (year)	41.8 $\pm$ 7.1	40.8 $\pm$ 7.0	0.21	58.9 $\pm$ 7.7	58.4 $\pm$ 7.9	0.62
<b>Area of residence</b>			0.35			0.33
Urban	113 (70.2)	102 (67.5)		91 (65.5)	102 (68.5)	
Rural	48 (29.8)	49 (32.5)		48 (34.5)	47 (31.5)	
<b>Educational level</b>			0.31			0.88
Illiterate	91 (56.5)	85 (56.3)		109 (78.4)	115 (77.2)	
Elementary /Koranic school	33 (20.5)	33 (21.9)		18 (12.9)	21 (14.1)	
Secondary school	28 (17.4)	18 (11.9)		9 (6.5)	10 (6.7)	
High school /University	9 (5.6)	15 (9.9)		3 (2.2)	3 (2.0)	
<b>Wealth score</b>	6.0 $\pm$ 1.8	7.6 $\pm$ 1.7	<0.01	5.8 $\pm$ 1.7	7.5 $\pm$ 1.6	<0.01
<b>Family history of breast cancer</b> <sup>a</sup>			0.05			0.04
Yes	13 (8.1)	5 (3.3)		15 (10.8)	7 (4.7)	
No	148 (91.9)	146 (96.7)		124 (89.2)	142 (95.3)	
<b>Age at menarche</b> (year)	13.4 $\pm$ 1.6	13.7 $\pm$ 1.2	0.07	13.6 $\pm$ 1.9	13.7 $\pm$ 1.1	0.49
<b>Age at first full-term pregnancy</b> <sup>b</sup> (year)	23.4 $\pm$ 5.7	21.2 $\pm$ 5.0	<0.01	22.5 $\pm$ 6.5	20.1 $\pm$ 5.3	<0.01
<b>Number of live births</b>			<0.01			0.03
Nulliparous	44 (27.3)	9 (6.0)		25 (18.0)	12 (8.1)	
1 to 3	74 (46.0)	82 (54.3)		45 (32.4)	48 (32.2)	
$\geq$ 4	43 (26.7)	60 (39.7)		69 (49.6)	89 (59.7)	
<b>History of breastfeeding</b>			<0.01			0.02
Yes	114 (70.8)	140 (92.7)		111 (79.9)	133 (89.3)	
No	47 (29.2)	11 (7.3)		28 (20.1)	16 (10.7)	
<b>History of oral contraceptive</b>			<0.01			<0.01
Ever	106 (65.8)	74 (49.0)		76 (54.7)	33 (22.1)	
Never	55 (34.2)	77 (61.0)		63 (45.3)	116 (77.9)	
<b>Age at menopause</b> <sup>c</sup> (year)				48.4 $\pm$ 4.4	47.1 $\pm$ 3.8	0.01
<b>Smoking</b>			0.04			0.04
Ever	7 (4.3)	1 (0.7)		6 (4.3)	1 (0.7)	
Never	154 (95.7)	150 (99.3)		133 (95.7)	148 (99.3)	
<b>Alcohol</b>			0.34			0.28
Ever	3 (1.9)	1 (0.7)		3 (2.1)	1 (0.7)	
Never	158 (98.1)	150 (99.3)		136 (97.8)	148 (99.3)	
<b>Physical activity</b> <sup>d</sup> (MET-hours/week)	131.6 $\pm$ 51.5	186.6 $\pm$ 71.9	<0.01	122.2 $\pm$ 64.1	168.7 $\pm$ 81.4	<0.01
<b>Energy intake</b> (kcal/day)	3098.7 $\pm$ 727.4	2968.0 $\pm$ 639.6	0.09	2960.7 $\pm$ 761.7	2847.1 $\pm$ 735.0	0.19
<b>BMI</b> (kg/m <sup>2</sup> )	28.0 $\pm$ 4.6	28.2 $\pm$ 5.9	0.82	29.9 $\pm$ 5.0	28.3 $\pm$ 4.8	<0.01
<b>Height</b> (cm)	160.8 $\pm$ 6.1	158.7 $\pm$ 7.2	<0.01	158.5 $\pm$ 7.1	157.7 $\pm$ 6.9	0.35
<b>Weight</b> (kg)	72.6 $\pm$ 12.5	70.6 $\pm$ 11.8	0.15	75.0 $\pm$ 13.1	70.3 $\pm$ 12.4	<0.01
<b>Waist-to-hip ratio</b>	0.87 $\pm$ 0.06	0.85 $\pm$ 0.08	0.04	0.91 $\pm$ 0.08	0.88 $\pm$ 0.08	<0.01
<b>Waist circumference</b>	88.5 $\pm$ 11.0	82.4 $\pm$ 11.6	<0.01	94.0 $\pm$ 12.0	85.5 $\pm$ 12.4	<0.01
<b>Hip circumference</b>	101.6 $\pm$ 10.9	96.9 $\pm$ 14.0	<0.01	103.3 $\pm$ 12.0	97.1 $\pm$ 12.3	<0.01

<sup>a</sup> First- and second-degree relatives.

<sup>b</sup> Among parous women.

<sup>c</sup> Among postmenopausal women.

<sup>d</sup> Physical activities (including occupational, recreational and household activities).

**Table 2: Association between anthropometric measurements and breast cancer risk in the BreCaFes Study.**

	Premenopausal (161/151)			Postmenopausal (139/149)			
	Ca /Co	OR <sup>a</sup> (95% CI)	OR <sup>b</sup> (95% CI)	Ca /Co	OR <sup>a</sup> (95% CI)	OR <sup>b</sup> (95% CI)	
<b>Current BMI</b>							
<25 kg/m <sup>2</sup>	43/41	1		<25 kg/m <sup>2</sup>	26/39	1	
25 – 29 kg/m <sup>2</sup>	64/64	1.49 (0.70-3.16)		25 – 29 kg/m <sup>2</sup>	49/59	0.99 (0.43-2.32)	
≥30 kg/m <sup>2</sup>	54/46	1.78 (0.79-4.02)		≥30 kg/m <sup>2</sup>	64/51	1.64 (0.72-3.75)	
p trend		0.33		p trend		0.08	
<b>Height (cm)</b>							
T1 <156	34/44	1	1	T1 <155	42/44	1	
T2 [156-162[	55/56	1.12 (0.50-2.48)	1.21 (0.54-2.71)	T2 [155-160[	40/54	0.82 (0.36-1.83)	0.82 (0.36-1.85)
T3 ≥162	72/51	1.05 (0.47-2.33)	1.15 (0.51-2.58)	T3 ≥160	57/51	0.62 (0.29-1.34)	0.71 (0.32-1.57)
p trend		0.40	0.19	p trend		0.46	0.79
<b>Weight (kg)</b>							
T1 <65	41/42	1	1	T1 <63	24/43	1	1
T2 [65-75[	54/55	1.14 (0.52-2.48)	1.08 (0.46-2.50)	T2 [63-75[	47/55	1.16 (0.49-2.70)	0.82 (0.32-2.10)
T3 ≥75	66/54	1.52 (0.70-3.27)	1.36 (0.49-3.74)	T3 ≥75	68/51	1.41 (0.62-3.19)	0.63 (0.18-2.16)
p trend		0.05	0.05	p trend		0.17	0.77
<b>Waist-to-hip</b>							
T1 <0.83	43/51	1	1	T1 <0.85	22/54	1	1
T2 [0.83-0.89[	48/44	2.48 (1.12-5.48)	2.54 (1.14-5.63)	T2 [0.85-0.90[	35/43	2.67 (1.11-6.43)	2.55 (1.04-6.22)
T3 ≥0.89	70/56	1.85 (0.88-3.89)	1.85 (0.88-3.89)	T3 ≥0.90	82/52	2.64 (1.18-5.86)	2.52 (1.13-5.63)
p trend		0.11	0.09	p trend		<b>0.28</b>	<b>0.29</b>
<b>Waist circumference (cm)</b>							
T1 <76.6	26/50	1	1	T1 <81.0	15/50	1	1
T2 [76.6-86.0[	33/43	1.07 (0.44-2.60)	1.13 (0.45-2.82)	T2 [81.0-91.0[	33/51	1.63 (0.63-4.15)	1.62 (0.63-4.18)
T3 ≥86.0	102/58	<b>2.92 (1.33-6.42)</b>	<b>3.26 (1.33-7.96)</b>	T3 ≥91.0	91/48	<b>4.46 (1.86-10.66)</b>	<b>4.43 (1.70-11.58)</b>
p trend		<b>&lt;0.01</b>	<b>&lt;0.01</b>	p trend		<b>&lt;0.01</b>	<b>&lt;0.01</b>
<b>Hip circumference (cm)</b>							
T1 <92.6	32/50	1	1	T1 <94.0	22/49	1	1
T2 [92.6-101.0[	34/50	1.06 (0.46-2.42)	1.13 (0.48-2.63)	T2 [94.0-100.0[	29/39	2.46 (0.92-6.53)	2.45 (0.91-6.53)
T3 ≥101.0	95/51	<b>3.00 (1.42-6.33)</b>	<b>3.56 (1.50-8.47)</b>	T3 ≥100.0	88/61	<b>4.08 (1.76-9.42)</b>	<b>3.97 (1.53-10.28)</b>
p trend		<b>0.01</b>	<b>&lt;0.01</b>	p trend		<b>&lt;0.01</b>	<b>&lt;0.01</b>
<b>Young-adult BMI (kg/m<sup>2</sup>)</b>							
T1 <19.8	33/47	1	1	T1 <19.8	34/46	1	1
T2 [19.8-23.2[	59/47	1.52 (0.69-3.37)	1.50 (0.66-3.41)	T2 [19.8-22.6[	34/44	0.99 (0.41-2.39)	0.92 (0.38-2.26)
T3 ≥23.2	52/46	2.13 (0.92-4.95)	2.09 (0.83-5.23)	T3 ≥22.6	57/48	1.71 (0.75-3.89)	1.34 (0.52-3.45)
Missing	17/11			Missing	14/11		
p trend		0.97	0.43	p trend		0.06	0.30
<b>Weight gain since the age of 20<sup>c</sup> (kg)</b>							
T1 <11.0	39/44	1	1	T1 <11.0	23/43	1	1
T2 [11.0-19.6[	54/46	1.28 (0.55-2.95)	1.29 (0.54-3.07)	T2 [11.0-20.0[	37/41	1.02 (0.42-2.47)	0.85 (0.34-2.13)
T3 ≥19.6	46/44	1.45 (0.60-3.49)	1.48 (0.50-4.36)	T3 ≥20.0	59/53	1.38 (0.59-3.19)	0.78 (0.26-2.33)
Missing	17/11			Missing	14/11		
p trend		0.14	0.22	p trend		0.47	0.42

<sup>a</sup> Odds ratios estimated by unconditional logistic regression and adjusted for age (continuous), area of residence (urban/rural), wealth score (continuous), number of live births (nulliparous, 1 to 3, ≥4), history of oral contraceptives (yes, no), history of breastfeeding (yes, no), age at first full-term pregnancy (nulliparous, <20 years, ≥20 years) and physical activity (continuous).

<sup>b</sup> Additional adjustment for current BMI (continuous).

<sup>c</sup> For woman who gained or maintained weight.



**Table 3: Association between early-life reported silhouette and breast cancer risk in the BreCaFez Study.**

	Premenopausal (161/151)		Postmenopausal (139/149)	
	Ca /Co	OR <sup>a</sup> (95% CI)	Ca /Co	OR <sup>a</sup> (95% CI)
<b>Silhouette at 6-11 years</b>				
Lean (Figure 1)	37/29	1	26/18	1
Medium (Figure 2)	90/65	0.86 (0.39-1.91)	68/69	0.75 (0.30-1.87)
Large (Figure 3–9)	26/56	<b>0.31 (0.12-0.80)</b>	40/60	0.40 (0.15-1.07)
Missing	8/1		5/2	
p trend		<b>0.01</b>		0.05
<b>Silhouette at 12-18 years</b>				
Lean (Figure 1–2)	41/66	1	28/62	1
Medium (Figure 3)	72/45	1.81 (0.85-3.84)	51/61	1.56 (0.71-3.42)
Large (Figure 4–9)	40/39	1.07 (0.46-2.49)	55/24	2.37 (0.99-5.68)
Missing	8/1		5/2	
p trend		0.91		0.05

<sup>a</sup> Odds ratios estimated by unconditional logistic regression and adjusted for age (continuous), area of residence (urban/rural), wealth score (continuous), number of live births (nulliparous, 1 to 3, ≥4), history of oral contraceptives (yes, no), history of breastfeeding (yes/no), age at first full-term pregnancy (nulliparous, <20 years, ≥20 years), physical activity (continuous) and current BMI (continuous).

**Table 4: Association between trajectories of body size and breast cancer risk in the BreCaFez Study.**

Trajectories	Premenopausal (151/149)		Postmenopausal (132/146)	
	Ca /Co	OR <sup>a</sup> (95% CI)	Ca /Co	OR <sup>a</sup> (95% CI)
<b>T 1: Low increase</b>	26/65	1	20/56	1
<b>T 2: Moderate increase</b>	89/57	<b>3.01 (1.36-6.63)</b>	64/73	1.71 (0.77-3.80)
<b>T 3: Strong increase</b>	37/27	<b>2.74 (1.03-7.26)</b>	48/17	<b>3.56 (1.34-9.44)</b>

<sup>a</sup> Odds ratios estimated by unconditional logistic regression and adjusted for age (continuous), area of residence (urban/rural), wealth score (continuous), number of live births (nulliparous, 1 to 3, ≥4), history of oral contraceptives (yes, no), history of breastfeeding (yes/no), age at first full-term pregnancy (nulliparous, <20 years, ≥20 years), physical activity (continuous) and current BMI (continuous).

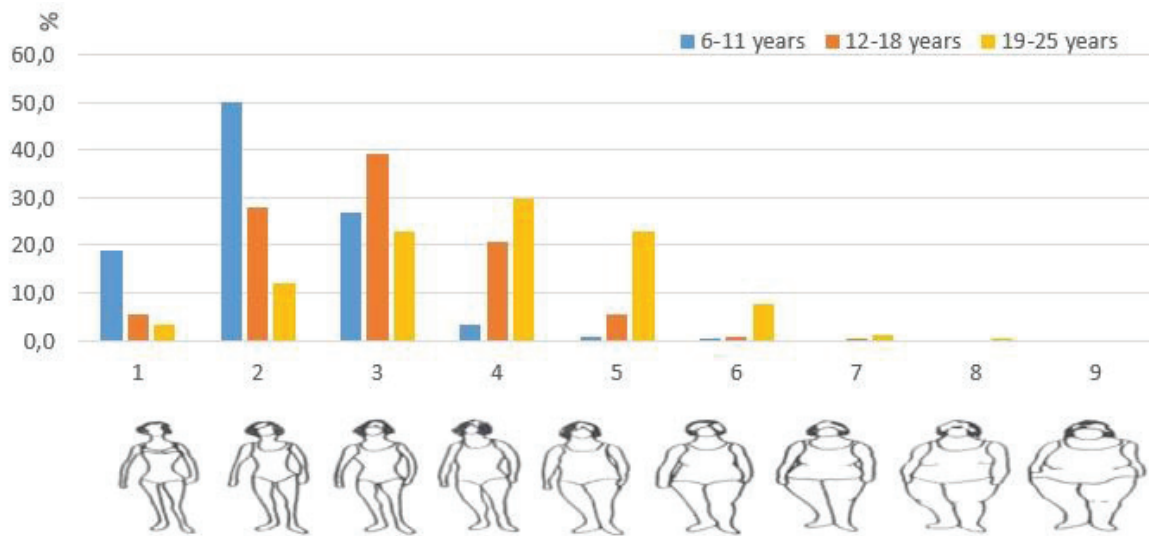


Figure 1: Distribution of the study population by reported silhouettes for different ages, the BreCaFez Study.

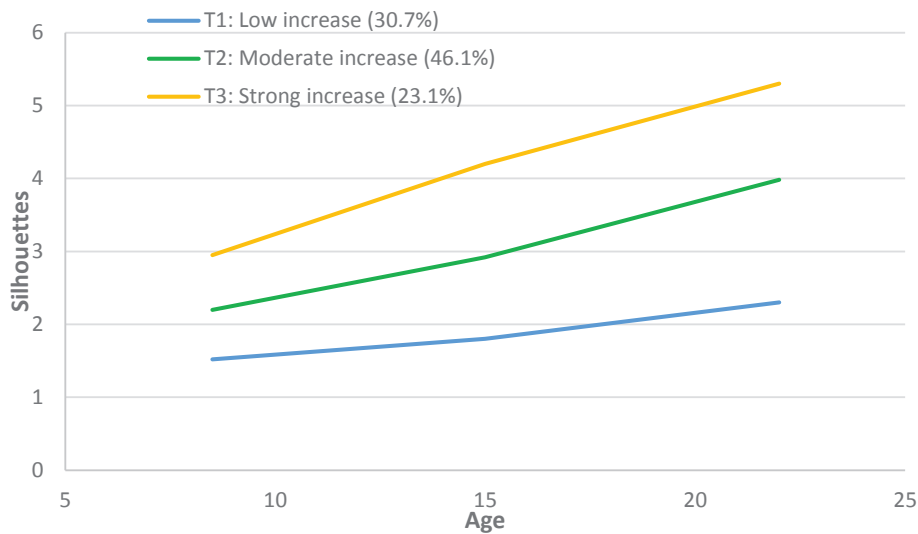


Figure 2: Estimated trajectories of body size by age, the BreCaFez Study.

## **5. Profession et risque de cancer du sein chez les femmes de la région de Fès, Maroc**

### **5.1. Introduction**

Nous avons vu dans les chapitres précédents que certains facteurs de risque de cancer du sein identifiés dans les pays industrialisés sont également retrouvés chez les femmes marocaines.

Cependant, ces facteurs seuls ne peuvent pas expliquer la survenue de la totalité des cas de cancer du sein [136]. D'autres facteurs de risque d'origine environnementale ou professionnelle sont également susceptibles d'être impliqués dans la survenue de ce cancer [70,137,138].

Ainsi, plusieurs études récentes suggèrent le rôle probable de l'exposition aux radiations ionisantes, champs électromagnétiques, travail de nuit et certains perturbateurs endocriniens, dans la survenue de cancer du sein [70,137,139]. Mais, une certaine controverse demeure concernant les conclusions de ces études.

En outre, des associations entre certaines professions et le risque de cancer du sein ont été rapportées dans la littérature. Certaines études suggèrent un risque augmenté de cancer du sein chez les femmes ayant exercé certaines professions, comme la profession d'infirmière, les professions de santé, hôtesses de l'air, et des professions dans le secteur d'agriculture [70,140–144]. Toutefois, les résultats des études explorant l'association entre les professions occupées par la femme et le risque de cancer du sein restent contradictoires.

Au Maroc, l'augmentation de l'incidence du cancer du sein constatée durant les dernières décennies a coïncidé avec un accès de plus en plus croissant des femmes marocaines à l'emploi, ainsi qu'à des professions auparavant réservés aux hommes. Le nombre de femmes actives âgées de 15 ans et plus est passé de 2,74 à 3,04 millions entre 2000 et 2012, soit une augmentation annuelle moyenne de 0,9% [145].

Ainsi, il semble pertinent d'explorer le rôle des facteurs professionnels dans la survenue de cancer du sein dans notre contexte marocain. Généralement, les études antérieures ayant comme objectif d'évaluer le risque de cancer du sein en fonction de la profession ont été réalisées dans les pays développés, et les données concernant les femmes dans des pays en voie de développement sont très rares.

L'objectif de ce travail était d'étudier l'association entre le métier, le secteur d'activité et le risque de cancer du sein chez les femmes marocaines dans la région de Fès.

### **5.2. Méthodes**

Les analyses de ce chapitre reposent sur les données de l'étude "BreCaFes Study".

Un questionnaire professionnel détaillé a été utilisé pour collecter les données concernant chaque emploi occupé pour une durée supérieure à 6 mois au cours de la carrière.

Dans cette étude, la classification des professions a été effectuée à l'aide de « la Classification Internationale Type des Professions (CITP 08) » et de « la Nomenclature Analytique des

Professions au Maroc (NAP 2001) ». La classification de secteur d'activité a été réalisée selon « la Nomenclature statistique des Activités économiques dans la Communauté Européenne (NACE Rév. 2008) ».

Les odds ratios (OR) et leurs intervalles de confiance à 95% ont été estimés à partir de régressions logistiques conditionnelles et non conditionnelles, en ajustant sur les variables de confusion.

### **5.3. Principaux résultats**

Dans les analyses par profession, nous observons que les femmes ayant travaillées comme ouvrière agricole avaient un risque élevé de cancer du sein (CITP 9211, NAP 7218 : OR = 4,69, IC 95% : 1,12–19,56), comparativement aux femmes n'ayant jamais travaillé dans cette profession. Une augmentation significative de ce risque en fonction de la durée de l'emploi dans cette profession a été également observée (p tendance = 0,04).

Les analyses par secteur d'activité montrent que les femmes ayant travaillé dans le secteur de la culture et production animale avaient un risque élevé de cancer du sein (NACE 01 : OR = 2,22, IC 95% : 1,09–4,52), comparativement aux femmes ayant jamais travaillées dans ce secteur.

### **5.4. Forces et faiblesses de l'étude**

À notre connaissance, cette étude était la première à étudier le lien entre la profession et le secteur d'activité et le risque de cancer du sein chez les femmes au Maroc et dans la région du nord de l'Afrique.

Elle présente néanmoins certaines limites. Une importante limite de cette étude est le faible nombre de femmes dans certaines professions et secteurs d'activités, et la stratification sur la durée d'emploi a accentué cette limite. Ainsi, certains intervalles de confiance étaient très larges. En outre, le risque de cancer du sein était diminué pour les femmes au foyer comparativement aux femmes ayant une histoire professionnelle. Étant donné que la fréquence de la parité était environ deux fois plus élevée chez les femmes au foyer que chez les femmes ayant une histoire professionnelle, une confusion résiduelle due aux facteurs reproductifs malgré l'ajustement sur ces facteurs peut être à l'origine de cette observation.

### **5.5. Conclusion**

Cette étude a permis de d'identifier certaines professions et secteur d'activité associées à un risque élevé de cancer du sein chez les femmes de notre région. Ainsi, ces données constituent une première étape pour l'exploration du rôle potentiel des expositions professionnelles dans l'augmentation du risque de cancer du sein chez certaines catégories de la population.

Ces résultats nous incitent à proposer des études épidémiologiques plus approfondies avec des méthodes d'évaluation de l'exposition professionnelle détaillées pour mieux élucider le rôle des expositions professionnelles dans la survenue de cancer du sein chez les femmes marocaines.

## 5.6. Article 5

### Occupation and risk of female breast cancer: A case-control study in Morocco.

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### Occupation and risk of female breast cancer: A case-control study in Morocco.

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## **Abstract**

**Background:** Breast cancer (BC) is the most frequent cancer among Moroccan women. Environmental and occupational factors may play a role in BC etiology. This study aimed to investigate the association between occupation, industry, and BC risk among Moroccan women.

**Methods:** We conducted a case–control study in the Fez region- Morocco. Cases were 300 newly-diagnosed histopathologically confirmed BC at the University Hospital in Fez. Controls were 300 randomly selected healthy women recruited from 6 health centers in Fez. Full occupational history was collected, with detailed description of each job held for at least 6 months. Occupations were coded according to the International Standard Classification of Occupations (08) and the Moroccan Analytical Classification of Professions (2001). Industries were coded according to the Statistical Classification of Economic Activities in the European Community (2008). Odds ratios and 95% confidence intervals, adjusted for potential confounders were estimated by using conditional and unconditional logistic regression.

**Results:** We found a significantly increased risk of BC among women employed in specific agricultural occupations, particularly those who worked as crop farm laborers (ISCO 08 code: 9211; OR= 4.69, 95% CI: 1.12–19.56) and the risk increased with duration of employment ( $p$  trend= 0.04). Analyses by industry corroborated these findings.

**Conclusions:** Our findings suggest that occupational exposures may be associated with increased risk of BC among female agricultural workers in this population. Further investigations, with advanced methods of occupational exposure assessment, are warranted to clarify the role of chemicals involved in this high-risk occupation and to suggest preventive actions and screening.

**Keywords:** Breast cancer, Occupation, Agricultural workers, Case–control study, Morocco.

## 1. Introduction

Breast cancer is the most common cancer and the leading cause of cancer death among women worldwide. Breast cancer accounts for 24.2% of all new cancer cases and 15% of all cancer-related deaths among females.<sup>1</sup> In Morocco, this disease accounts for 35.8% of all malignant tumors in women.<sup>2</sup> Although breast cancer is relatively less frequent in Morocco compared to some Western countries,<sup>3</sup> the age standardized incidence rate increased from 35.0 to 49.5 per 100 000 women between 2004 and 2012, showing an annual increase of 3.18%.<sup>2</sup> This increase may be partially attributed to improvements in screening programs,<sup>4</sup> but it can be widely explained by changes in the pattern of cancer risk factors in Moroccan women.<sup>3</sup>

Breast cancer risk is multifactorial and the established risk factors for the development of the disease include reproductive and hormonal factors, family history, genetic predisposition and unhealthy lifestyle including obesity (in postmenopausal women) and alcohol consumption,<sup>5,6</sup> but these factors do not fully explain breast cancer etiology. Recently, results from several studies show that environmental and occupational factors may also play a role in breast cancer development, although these results are controversial.<sup>7-10</sup>

Globally, women may experience appreciable exposures to a wide range of occupational agents in work environments that could influence breast cancer development through direct or indirect mechanisms.<sup>9,11</sup> Although the evidence is inconsistent, occupational exposure to nightshift work, ionizing radiation, electromagnetic fields and endocrine-disrupting chemicals (including chlorinated hydrocarbons, organic solvents, dichlorodiphenyltrichloroethane (DDT) and organochlorine pesticides) have been hypothesized to be potential risk factors for human breast cancer.<sup>7,8,10-12</sup> Some previous studies have identified increased risks of female breast cancer in specific occupations such as nurses and medical/health care professionals, agriculture workers, flight attendants and some other white-collar workers.<sup>10,13-17</sup> However, findings from studies on breast cancer and occupations have generally been inconclusive or inconsistent.

In Morocco, the number of women in employment has increased in recent decades. It grew up from 2.74 million in 2000 to 3.04 million in 2012, with an annual increase of 0.9%.<sup>18</sup> Moreover, women are more likely to hold jobs that were previously reserved for men in the first half of the

20th century. However, the contributions of occupational factors in breast cancer risk among Moroccan women remain poorly documented. In addition, most previous studies on occupational breast cancer risk were conducted in Western populations and data from developing countries is extremely scarce. The aim of this study was to explore the associations between occupation, industry, and breast cancer risk in Moroccan women in the Fez region.

## **2. Methods**

### **2.1. Study Population**

*The BreCaFez Study* is a case–control study, conducted in the Fez region- Morocco, from February 2016 until August 2017. A total of 300 incident breast cancer cases and 300 controls were recruited in the study. The design of the study has been described in detail elsewhere.<sup>19</sup>

Briefly, cases were recruited from the Medical Oncology Center of the University Hospital in Fez. The cases were included according to the following criteria: (a) newly-diagnosed histologically-confirmed in situ or invasive breast cancer, (b) had not received any treatment, such as radiotherapy, chemotherapy or anti-estrogens (e.g., tamoxifen), (c) were not suffering from chronic kidney failure, (d) were not pregnant or nursing, and (e) were able to give informed consent. The response rate for cases was 96.7% (300/310). The reasons for refusal were mainly lack of time for interview or feeling tired. Controls were randomly selected among healthy women with no previous history of cancer, visiting one of six outpatient primary health centers in the Fez region. Control subjects were matched individually to the cases by age [ $\pm 5$  years (72% of pairs matched by age  $\pm 1$  year)] and area of residence (urban vs. rural). Women who accompanied patients with any type of cancer were ineligible for recruitment as controls.

The response rates among eligible women were 96.7% for cases and 87.9% for controls.

### **2.2. Data collection**

Participants were interviewed at enrolment in the study by four interviewers who were trained in conducting interviews in a standardized way. Data were collected using an in depth questionnaire to collect information about sociodemographic and anthropometric characteristics, family history of cancer including breast cancer, menstrual and reproductive



history (e.g., age at menarche, age at first full-term pregnancy, parity, menopausal status, age at menopause, history of breastfeeding), hormone use, smoking, alcohol consumption, physical activity and dietary habits. Full occupational history was collected, with a detailed description of each job held for at least 6 months (since leaving school). The occupational questionnaire included data on the sector of activity, the start date, date of termination, department, job title, task description, self-reported exposures, machines and materials used, etc.

Occupations were coded according to the International Standard Classification of Occupations (ISCO 08) and the Moroccan Analytical Classification of Professions (Nomenclature analytique des professions, NAP 2001). Industries were coded according to the Statistical Classification of Economic Activities in the European Community, Rev.2 (NACE 2008), which is similar to the Moroccan Classification of Activities (Nomenclature Marocaine des Activités -NMA 2010) regarding the first three digits of the code. For each job, the coding was based on job title and task description of the participants. All coding was conducted blind to the case–control status of the participants.

Socio-economic status of participants was assessed using a validated wealth score based on household assets including electricity, television, cell phone, refrigerator, indoor bath or shower, indoor tap, flush toilet, washing machine, car and landline phone.<sup>20</sup> The questionnaire also assessed physical activity of women in the last 12 months, as described in detail elsewhere.<sup>19</sup> In this study, we quantified the intensity of physical activity using a MET- hours per week of all activities combined, including occupational, recreational and household activities. Total MET-hours per week for each category of activity were calculated by multiplying the number of hours per week spent by the MET score corresponding to that category. Postmenopausal status was defined as self-reported absence of menstruation in the last 12 months.

### **2.3. Statistical analysis**

Descriptive statistics (means for continuous variables and frequencies for categorical variables) summarizing subject characteristics were calculated. Conditional logistic regression models were used to estimate the odds ratio (OR) and 95% confidence interval (CI) for ever being employed in a specific occupation or industry compared with no employment in that occupation or industry

(reference category). Only ORs for occupations or industries that included more than five cases and five controls were calculated. Multivariate adjusted ORs and corresponding 95% CIs were estimated, adjusting for number of live births (nulliparous, 1 to 3,  $\geq 4$ ), menopausal status combined with age at menopause (premenopausal, postmenopausal  $\leq 47$  years, and postmenopausal  $>47$  years), history of oral contraceptives (yes, no), family history of breast cancer (yes/no), history of breastfeeding (never, ever), wealth score (continuous), age at first full-term pregnancy (nulliparous,  $<20$  years,  $\geq 20$  years) and physical activity (continuous). Median values in controls were used as cut-off points for age at menopause and number of live births.

Further analyses were also conducted to assess the effect of duration of employment in certain occupation or industry (never employed in the occupation or industry of interest,  $<10$  years,  $\geq 10$  years). The reference group was women who were never employed in the occupation or industry of interest. In these stratified analyses, ORs and 95% CI were estimated using unconditional logistic regression and adjusted for the above variables and age (continuous) and area of residence (urban/rural). Test for trend was performed by using duration of employment as a continuous variable in the model.

In this study, due to the very low frequency of postmenopausal hormone use, this variable was excluded from the analysis. Models were ran with and without this variable and the results were similar. Data analysis was performed using SPSS, version 20 software. In all statistical analyses, p-values were two-sided and considered statistically significant if lower than 0.05.

### **3. Results**

The distribution of the selected baseline characteristics of cases and controls are shown in table 1. The mean age ( $\pm$ SD) of cases and controls were 49.7 ( $\pm 11.3$ ) and 49.5 ( $\pm 11.5$ ) years, respectively. Compared with controls, cases were more likely to be older at first full-term pregnancy and at age of menopause, and to have a lower number of live births, a shorter duration of breastfeeding, family history of breast cancer, history of oral contraceptive use and lower wealth score, and less likely to be physically active. Cases and controls did not show differences in educational level, menopausal status, age at menarche and BMI.

The multivariate-adjusted ORs by occupation, industry and duration of employment (<10 year, ≥10 years) are shown in Table 2. About 46.3% of the cases and 79.3% of controls were reported to be housewives, and this category had a significant low risk of breast cancer (OR = 0.36, 95% CI: 0.19–0.67).

#### *Risk by ISCO 08 code*

An elevated risk of breast cancer was observed for workers in “Elementary occupations” (OR=3.15, 95% CI: 1.51–6.57), particularly among women employed as crop farm labourers (ISCO 08 code: 9211; OR=4.69, 95% CI: 1.12–19.56), with a significant positive trend for women who worked for 10 or more years as compared to those who never employed in this occupation (p trend = 0.04). No other occupational group (ISCO 08 code) demonstrated a significantly increased risk of breast cancer.

#### *Risk by NAP code*

Similarly, an increased risk of breast cancer was observed for “Agricultural and fishery workers” (OR=2.22, 95% CI: 1.09–4.52), in particular for multi-skilled crop workers (NAP code: 7218; OR=4.69, 95% CI: 1.12–19.56), with a significant trend for duration of employment (p trend = 0.04). No other occupational group (NAP code) showed a significantly increased risk of breast cancer.

#### *Risk by NACE code*

Industry results were similar to occupation results; we observed a significantly increased risk of breast cancer for women employed in related agricultural occupations (OR=2.22, 95% CI: 1.09–4.52), particularly in growing of non-perennial crops sector (NACE code: A011; OR=4.69, 95% CI: 1.12–19.56), which also showed an elevated risk for duration of employment (p trend = 0.04). No other industrial group demonstrated a significantly increased risk of breast cancer.

## **4. Discussion**

To the best of our knowledge, this is the first study that aimed to investigate the risk of breast cancer among different occupational and industrial groups in Morocco. The study findings suggest an increased risk of breast cancer for women employed in agricultural occupations, particularly

women who worked as crop farm laborers, with a significantly positive trend for duration of employment.

Our findings are consistent with previously published studies conducted in developed countries suggesting an increased risk of breast cancer among women with an occupational history of farming/agricultural work.<sup>15,21-25</sup> For instance, a Canadian case-control study reported an elevated breast cancer risk among women who had been employed in agriculture (OR = 1.36, 95% CI: 1.01–1.82).<sup>15</sup> A population-based case-control study conducted in British Columbia reported an increased risk of breast cancer among pre- and post-menopausal women employed as crop farmers (OR = 10.3, 90% CI: 1.71–62.6) or in fruit and vegetable farming (OR = 3.11, 90% CI: 1.24–7.81).<sup>21</sup> In an Italian population-based study, Salerno et al. found that employment as farmer was associated with an increased risk of breast cancer (OR = 1.72, 95% CI: 1.03–2.84).<sup>22</sup> In Ontario, Canada, Brophy et al. reported an increased risk among women with an occupational history of farming (OR = 2.8, 95% CI: 1.6–4.8).<sup>23</sup> In Shanghai- China, Gardner et al. found that women employed as farmers for over 10 years were twice as likely to develop breast cancer (OR = 2.08, 95% CI: 1.15–3.74).<sup>24</sup> In California, USA, Mills & Yang found a six-fold excess risk for breast cancer among women who farmed mushrooms (OR = 6.02, 95% CI: 2.01–18.00).<sup>25</sup> In North Carolina, USA, Duell et al. observed an increased risk of breast cancer among a subgroup of farming women who were exposed to pesticides.<sup>26</sup> The US Agricultural Health Study cohort reported also an elevated risk of postmenopausal breast cancer among women living close to pesticide application areas.<sup>27</sup>

The increased risk of breast cancer among agricultural workers might be related to exposure to pesticides during farming activities. The exposure to pesticides mainly occurs during preparation and application of the pesticide solutions and during loading and cleaning-up of used equipment. However, farmers may be also exposed to pesticides in other agricultural tasks not related directly to the use of pesticides, such as farmers performing manual labor in areas treated by pesticides or contacting pesticide residues on the crop or soil.<sup>28</sup> Several environmental chemicals, including pesticides, act as mammary carcinogens in animal studies, activate relevant hormonal pathways, or enhance mammary gland susceptibility to carcinogenesis.<sup>7,29</sup> The potential of certain pesticides to act as endocrine disrupting chemicals (EDCs) has been recently considered.<sup>30</sup> Some chemical compounds such as organochlorines and dichlorodiphenyltrichloroethane (DDT), widely used to

control harmful pests and prevent crop yield losses or product damage, have been classified as endocrine disruptors<sup>31</sup> and are suspected carcinogenic to the human breast<sup>32–34</sup>. It has been suggested that these estrogenic environmental compounds act like xenoestrogens in the body, interact with estrogen receptor, and increase the risk of breast cancer by increasing cellular proliferation.<sup>35,36</sup>

Many types of chemical pesticides that are non-patented, more toxic, and environmentally persistent, are used extensively in developing countries for many years.<sup>37</sup> In Morocco, pesticides are often not used in the proper way by farmers.<sup>38</sup> Moreover, the last report of the National Office of Food Safety of Morocco (ONSSA)<sup>39</sup> indicated that about 15% of pesticides that can be harmful for both human health and the environment are used by Moroccan farmers, though smuggled and not controlled. Further studies with detailed exposure assessments of chemical constituents, advanced methods of occupational exposure assessment and exposure time windows are needed to elucidate the role of pesticides in breast cancer etiology among Moroccan women.

In contrast, decreased risks of female breast cancer have been reported among women in farming/agricultural work in several other studies.<sup>14,34,40–42</sup> For instance, a recent population-based cohort of Nordic Occupational Cancer Study (NOCCA) reported that farmers had low risk of breast cancer with a standardized incidence ratio (SIR) of 0.80 (95% CI: 0.78–0.82).<sup>34</sup> Also, in the CECILE Study, Villeneuve et al. found decreased risk among females in agricultural workers (OR = 0.7, 90 % CI: 0.6–1.0).<sup>14</sup> Some of these studies suggest that the inverse association between farming/agricultural work and female breast cancer may be due to active and healthy lifestyles, habitually shown in female farmers, including high physical activity and diet high in fruits and vegetables. Probably, working conditions differ between countries and farmers in these populations benefit from the agriculture activities. However, it is possible that due to correct use and the control of pesticides in these countries they are not exposed to carcinogens in contrast to what is reported for our country.

While in this study there were no significant associations between other occupational or industrial groups and breast cancer risk except for agricultural workers, other occupational studies support the link between increased risk of developing breast cancer and working in jobs that involve

exposure to ionizing radiation, electromagnetic fields or night shift work. Many previous studies suggest an association between occupational ionizing radiation exposure and breast cancer risk.<sup>11,43,44</sup> The US Radiologic Technologist cohort study (including 106,953 female) reported a significantly elevated risk of breast cancer in female radiologic technologists who experienced a cumulative exposure to ionizing radiation, mainly among those who started working in the first half of the 20th century.<sup>45</sup> However, the International Agency for Research on Cancer (IARC) classification of X-radiation and gamma radiation as carcinogenic to the human breast was based on military and medical sources.<sup>10,12</sup> Otherwise, the results are mixed in occupational studies of women exposed to non-ionizing radiation (electromagnetic fields).<sup>10,46,47</sup> There is also growing evidence that night shift working is an important factor leading to increased risk of breast cancer. The IARC has classified shift work involving circadian rhythm disruption as probably carcinogenic to humans (Group 2A).<sup>48</sup> A recent meta-analysis reported a positive relationship between long-term night shift work and breast cancer risk (OR = 1.31, 95% CI: 1.19–1.44), with remarkable elevation of this risk among nurses (OR = 1.57, 95% CI: 1.23–2.01).<sup>49</sup>

There are limitations related to our study. First, the small sample size in many occupational groups may limit statistical power to detect certain associations. Also, stratification by duration of employment accentuated small numbers of subjects in each subgroup, and that lead to large confidence intervals. Thus, our results should be interpreted with caution. Second, due to the retrospective nature of this study, most of our data were reported by participants, and could be subject to recall bias. However, this is likely to be non-differential with regards to lifetime occupational history. Third, the concerns due to multiple testing that can lead to some chance findings. Fourth, globally, housewives had a significant low risk of breast cancer compared with others. Since, the frequency of parity was approximately 2 times higher in housewives vs. worker group (data not shown), despite adjustment for this factor the residual confounding effects of reproductive factors might possibly be one explanation for the protective effect observed among women in this category. Fifth, considering that, cases were significantly more likely to have a lower wealth score than controls, the possibility of selection bias cannot be ruled out in this study. However, this probable difference between cases and controls on socioeconomic level was shown

in our previous study<sup>50</sup> on breast cancer. It is therefore particularly important to investigate the relationship between the socioeconomic level and breast cancer risk in the Moroccan context.

This study has many several strengths. First, this is the first epidemiological study to investigate the association between occupations, industry and breast cancer risk among Moroccan women. Second, the selection of population-based controls in our study may have improved the representation of the Fez population. Third, the job coding was based on the full job and detailed task description for each job held by cases and controls, thus misclassification errors related to coding are very limited in this study. Fourth, the adjustment for potential confounders including socio-economic level was assessed by a validated wealth score. Fifth, the high participation rate, and as such reduced selection bias in both cases and controls can be considered as strength.

In conclusion, our findings indicate that women employed in agricultural occupations had an elevated risk of breast cancer compared to those who never worked in these occupations and the risk increased with duration of employment. Further investigations, with advanced methods of occupational exposure assessment, are warranted to clarify the role of chemical products involved in these high-risk occupations. Moreover, these occupational categories need more preventive actions to reduce exposure and help screening of at-risk groups.

**Authors' contributions:** MK, KE, CN and BC participated in the conception or design of the work. FA, HC, and NM participated in the acquisition of data. MK, KE, EF, VC, AM, CB, IH, AS, and BC participated in the analysis and interpretation of data. MK drafted the manuscript. KE, EF, VC, IH, IR, CN, AS, and BC critically revised the manuscript for important intellectual content. All authors contributed to the interpretation of the results, reviewed, and edited the final manuscript.

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**Disclaimer:** None

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**Table 1: Distribution of selected baseline characteristics of cases and controls (numbers and percentages; mean values and standard deviations) in the BreCaFez Study.**

Characteristics	Cases	Controls	<i>P</i> <i>difference</i>
	(n = 300)	(n = 300)	
<b>Area of residence</b>			0.53
Urban	204 (68.0)	204 (68.0)	
Rural	96 (32.0)	96 (32.0)	
<b>Educational level</b>			0.47
Illiterate	200 (66.7)	200 (66.7)	
Elementary /Koranic school	51 (17.0)	54 (18.0)	
Secondary school	37 (12.3)	28 (9.3)	
High school /University	12 (4.0)	18 (6.0)	
<b>Menopausal status</b>			0.23
Premenopausal	161 (53.7)	151 (50.3)	
Postmenopausal	139 (46.3)	149 (49.7)	
<b>Age of menopause<sup>a</sup> (year)</b>			<0.01
≤47	51 (36.7)	108 (72.5)	
>47	81 (58.3)	27 (18.1)	
Missing	7 (5.0)	14 (9.4)	
<b>Number of live births</b>			<0.01
Nulliparous	69 (23.0)	21 (7.0)	
1 to 3	119 (39.7)	130 (43.3)	
≥4	112 (37.3)	149 (49.7)	
<b>History of breastfeeding</b>			<0.01
Yes	225 (75.0)	273 (91.0)	
No	75 (25.0)	27 (9.0)	
<b>History of oral contraceptive</b>			<0.01
Yes	182 (60.7)	107 (35.7)	
No	118 (39.3)	193 (64.3)	
<b>Family history of breast cancer<sup>b</sup></b>			<0.01
Yes	28 (9.3)	12 (4.0)	
No	272 (90.7)	288 (96.0)	
<b>Smoking</b>			0.01
Past/ Current	13 (4.3)	2 (0.7)	
Never	287 (95.7)	298 (99.3)	
<b>Alcohol</b>			0.15
Ever	6 (2.0)	2 (0.7)	
Never	294 (98.0)	298 (99.3)	
<b>Age at entry (year)</b>	49.7 ± 11.3	49.5 ± 11.5	0.85
<b>Age at menarche (year)</b>	13.5 ± 1.7	13.7 ± 1.2	0.07
<b>Age at first full-term pregnancy<sup>c</sup> (year)</b>	22.9 ± 6.1	20.7 ± 5.1	<0.01
<b>BMI (kg/m<sup>2</sup>)</b>	28.9 ± 4.9	28.2 ± 5.4	0.11
<b>Physical activity<sup>d</sup> (MET-hours/week)</b>	127.2 ± 57.8	177.7 ± 77.2	<0.01
<b>Wealth score</b>	5.9 ± 1.7	7.6 ± 1.6	<0.01

<sup>a</sup> Among postmenopausal women.

<sup>b</sup> First- and second-degree relatives.

<sup>c</sup> Among parous women.

<sup>d</sup> Physical activities (including occupational, recreational and household activities).

**Table 2: Odds ratios and 95% confidence intervals for breast cancer by occupation (ISCO 08 code, NAP code), industry (NACE code), and duration of employment (<10 year; ≥10 years) in the BreCaFez Study.**

	Occupation (ISCO 08 code)	Ever employed		Duration of employment < 10 years		Duration of employment ≥10 years		P-trend
		Ca / Co	OR <sup>a,b</sup> (95% CI)	Ca / Co	OR <sup>a,c</sup> (95% CI)	Ca / Co	OR <sup>a,c</sup> (95% CI)	
	Housewife	139/238	0.36 (0.19-0.67)					
	<b>Occupation (ISCO 08 code)</b>							
1	Managers	0/1	—	—	—	—	—	—
2	Professionals	4/3	—	—	—	—	—	—
3	Technicians and associate professionals	4/4	—	—	—	—	—	—
4	Clerical support workers	9/4	—	—	—	—	—	—
5	Service and sales workers	9/3	—	—	—	—	—	—
7	Craft and related trades workers	12/12	1.44 (0.32-6.49)	5/3	2.20 (0.35-13.61)	7/9	1.15 (0.28-4.64)	0.63
7318	Handicraft worker in textile	2/3	—	—	—	—	—	—
7512	Bakers, pastry-cooks and confectionery makers	0/1	—	—	—	—	—	—
7531	Tailors, dressmakers, furriers and hatters	8/8	1.44 (0.23-8.92)	3/3	0.89 (0.09-8.24)	5/5	2.00 (0.28-14.01)	0.54
7534	Upholsterers and related workers	2/0	—	—	—	—	—	—
8	Plant and machine operators, and assemblers	7/1	—	—	—	—	—	—
9	Elementary occupations	126/35	<b>3.15 (1.51-6.57)</b>	23/7	2.46 (0.88-6.87)	103/28	<b>3.00 (1.62-5.55)</b>	<b>&lt;0.01</b>
9111	Domestic cleaners and helpers	21/4	—	—	—	—	—	—
9211	Crop farm labourers	25/6	<b>4.69 (1.12-19.56)</b>	4/2	0.84 (0.10-6.54)	21/4	<b>4.80 (1.14-20.25)</b>	<b>0.04</b>
9212	Livestock farm labourers	17/5	—	—	—	—	—	—
9213	Mixed crop and livestock farm labourers	70/19	1.42 (0.63-3.16)	11/3	2.80 (0.56-13.95)	59/16	1.81 (0.88-3.69)	0.07
9333	Freight handler	0/1	—	—	—	—	—	—
	<b>Occupation (NAP code)</b>							
1	Senior officials and members of the liberal professions	0/1	—	—	—	—	—	—
2	Middle-level officials	6/8	0.87 (0.15-5.03)	—	—	—	—	—
2421	Nurses	0/1	—	—	—	—	—	—
2521	Primary school teachers	1/1	—	—	—	—	—	—
2531	Early childhood educators	1/0	—	—	—	—	—	—

2591	Teaching professionals not elsewhere classified	2/1	—	—	—	—	—	—	—	—	—	—	—
2611	Administrative officers	2/3	—	—	—	—	—	—	—	—	—	—	—
2641	Computer professionals	0/2	—	—	—	—	—	—	—	—	—	—	—
<b>3</b>	<b>Clerks, employees</b>	12/6	1.09 (0.16-7.19)	6/2	1.12 (0.17-7.06)	6/4	1.99 (0.37-10.62)	0.43	—	—	—	—	—
3111	Keyboard operators, data entry clerks and secretaries	7/2	—	—	—	—	—	—	—	—	—	—	—
3113	Accounting and bookkeeping clerks	3/0	—	—	—	—	—	—	—	—	—	—	—
3121	Cashiers and ticket clerks	0/1	—	—	—	—	—	—	—	—	—	—	—
3122	Receptionists and client information workers	0/2	—	—	—	—	—	—	—	—	—	—	—
3212	Commercial sales representatives	1/0	—	—	—	—	—	—	—	—	—	—	—
3323	Waiters	1/1	—	—	—	—	—	—	—	—	—	—	—
<b>4</b>	<b>Business and finance professionals</b>	3/0	—	—	—	—	—	—	—	—	—	—	—
<b>6</b>	<b>Artisans and qualified craft workers</b>	17/12	2.12 (0.62-7.26)	5/3	2.34 (0.37-14.65)	12/9	2.87 (0.88-9.34)	0.05	—	—	—	—	—
6615	Baker, pastry-cooks, confectioner and chocolatiers	0/1	—	—	—	—	—	—	—	—	—	—	—
6714	Cooks	2/0	—	—	—	—	—	—	—	—	—	—	—
6731	Hairdressers	2/0	—	—	—	—	—	—	—	—	—	—	—
6734	Beauticians and related workers	1/0	—	—	—	—	—	—	—	—	—	—	—
6817	Crocheters and related workers	2/3	—	—	—	—	—	—	—	—	—	—	—
6822	Dressmakers and traditional tailors	8/8	1.44 (0.23-8.92)	3/3	0.89 (0.09-8.24)	5/5	2.00 (0.28-14.01)	0.54	—	—	—	—	—
6826	Upholsterers and related workers	2/0	—	—	—	—	—	—	—	—	—	—	—
<b>7</b>	<b>Agricultural and fishery workers</b>	111/30	<b>2.22 (1.09-4.52)</b>	19/6	2.39 (0.75-7.56)	92/24	<b>2.51 (1.33-4.75)</b>	<b>&lt;0.01</b>	—	—	—	—	—
7218	Multi-skilled crop workers	25/6	<b>4.69 (1.12-19.56)</b>	4/2	0.84 (0.10-6.54)	21/4	<b>4.80 (1.14-20.25)</b>	<b>0.04</b>	—	—	—	—	—
7231	Mixed crop and livestock farm labourers	70/19	1.42 (0.63-3.16)	11/3	2.80 (0.56-13.95)	59/16	1.81 (0.88-3.69)	0.07	—	—	—	—	—
7235	Livestock farm labourers	17/5	—	—	—	—	—	—	—	—	—	—	—
<b>8</b>	<b>Plant and machine operators, and assemblers</b>	7/1	—	—	—	—	—	—	—	—	—	—	—
<b>9</b>	<b>Non-agricultural workers, freight handlers and odd job persons</b>	21/5	—	—	—	—	—	—	—	—	—	—	—
<b>Industry (NACE code)</b>													
<b>A</b>	<b>Agriculture, forestry and fishing</b>	111/30	<b>2.22 (1.09-4.52)</b>	19/6	2.39 (0.75-7.56)	92/24	<b>2.51 (1.33-4.75)</b>	<b>&lt;0.01</b>	—	—	—	—	—
A011	Growing of non-perennial crops	25/6	<b>4.69 (1.12-19.56)</b>	4/2	0.84 (0.10-6.54)	21/4	<b>4.80 (1.14-20.25)</b>	<b>0.04</b>	—	—	—	—	—
A014	Animal production	17/5	—	—	—	—	—	—	—	—	—	—	—



A0150	Mixed farming	70/19	1.42 (0.63-3.16)	11/3	2.80 (0.56-13.95)	59/16	1.81 (0.88-3.69)	0.07
<b>B</b>	<b>Mining and quarrying</b>	1/0	—	—	—	—	—	—
<b>C</b>	<b>Manufacturing</b>	18/12	1.05 (0.26-4.23)	9/3	2.83 (0.53-14.95)	9/9	1.23 (0.33-4.55)	0.45
C1020	Processing and preserving of fish, crustaceans and mollusks	1/0	—	—	—	—	—	—
C1393	Manufacture of carpets and rugs	2/0	—	—	—	—	—	—
C1419	Manufacture of wearing apparel and accessories	11/9	1.24 (0.24-6.42)	5/3	1.33 (0.19-8.94)	6/6	1.53 (0.25-9.16)	0.58
C1439	Manufacture of other knitted and crocheted apparel	2/3	—	—	—	—	—	—
C1520	Manufacture of footwear	2/0	—	—	—	—	—	—
C2931	Manufacture of electrical and electronic equipment for motor vehicles	1/0	—	—	—	—	—	—
<b>G</b>	<b>Wholesale and retail trade; repair of motor vehicles and motorcycles</b>	4/3	—	—	—	—	—	—
<b>H</b>	<b>Transportation and storage</b>	0/1	—	—	—	—	—	—
<b>I</b>	<b>Accommodation and food service activities</b>	2/4	—	—	—	—	—	—
<b>J</b>	<b>Information and communication</b>	0/2	—	—	—	—	—	—
<b>M</b>	<b>Professional, scientific and technical activities</b>	4/1	—	—	—	—	—	—
<b>N</b>	<b>Administrative and support service activities</b>	0/1	—	—	—	—	—	—
<b>O</b>	<b>Public administration and defense; compulsory social security</b>	6/3	—	—	—	—	—	—
<b>P</b>	<b>Education</b>	4/2	—	—	—	—	—	—
<b>Q</b>	<b>Human health and social work activities</b>	1/1	—	—	—	—	—	—
<b>S</b>	<b>Other service activities</b>	4/0	—	—	—	—	—	—
<b>T</b>	<b>Activities of households as employers; undifferentiated goods-and services-producing activities of households for own use</b>	22/4	—	—	—	—	—	—

<sup>a</sup> ORs were calculated only for occupational and industrial categories that included more than five cases and five controls.

<sup>b</sup> Odds ratios estimated by conditional logistic regression and adjusted for number of live births (nulliparous, 1 to 3, ≥4), menopausal status combined with age at menopause (premenopausal, postmenopausal ≤47 years, and postmenopausal >47 years), history of oral contraceptives (yes, no), family history of breast cancer (yes/no), history of breastfeeding (never, ever), wealth score (continuous), age at first full-term pregnancy (nulliparous, <20 years, ≥20 years) and physical activity (continuous).

<sup>c</sup> Odds ratios estimated by unconditional logistic regression and adjusted for above variables and age (continuous) and area of residence (urban/rural).

## **6. Facteurs nutritionnels : Préparation et validation des outils pour l'analyse des données nutritionnelles**

Pour l'analyse et l'évaluation des données nutritionnelles de notre étude il était nécessaire, d'élaborer et de valider des outils pertinents pour cette analyse pour le contexte marocain. Il s'agit de la table de composition des aliments et du questionnaire de fréquence alimentaire (FFQ).

### **6.1. Mise à jour de la table de composition des aliments**

#### *6.1.1. Introduction*

Les tables de composition des aliments sont des sources de données qui indiquent les valeurs énergétiques, les nutriments et d'autres éléments importants tels les fibres pour chacun des aliments dans une population [146–149]. Les données sur la composition des aliments sont largement utilisées dans les domaines de la santé, la recherche scientifique, l'agriculture, l'industrie alimentaire et le commerce [150–153]. Elles servent également, pour la planification, l'élaboration de programmes d'éducation et le développement des recommandations en matière d'alimentation [154–156].

Les tables de composition des aliments sous forme imprimée constituent un outil traditionnel d'information et qui est actuellement remplacé par des versions électroniques sous forme de banques de données informatisées [157]. Les valeurs des tables de composition des aliments sont généralement basées sur des analyses chimiques des laboratoires ou sont estimées à partir d'autres données appropriées de la littérature [158–160].

Il est établi que la composition et les caractéristiques de certains aliments peuvent varier d'un pays à l'autre [160]. En outre, les valeurs nutritionnelles des aliments varient considérablement selon de nombreux facteurs incluant le sol, le climat, l'exposition au soleil, l'espèce animale et les cultivars végétaux, les conditions et les méthodes de culture et d'élevage, la préparation et le stockage des aliments [158,160,161]. Compte tenu de ces informations, il est primordial de développer des tables de composition des aliments adéquates pour chaque population.

Malheureusement, peu d'intérêt est accordé par les chercheurs Marocains au développement et à la mise à jour de la table de composition des aliments marocaine. De plus à l'heure actuelle, les études visant à explorer les associations entre l'alimentation et certaines maladies et tenant compte la composition et la valeur nutritionnelle des aliments, sont très rares au Maroc. Ceci, peut être expliqué partiellement par le manque de données fiables sur les compositions nutritionnelles des aliments dans notre pays.

A notre connaissance, la dernière mise à jour de la table de composition des aliments au Maroc a été effectuée par El Khayate R en 1984 [162]. Toutefois, les données de cette table sont devenues obsolètes et incomplètes. Ceci rend la mise à jour de la table de composition des aliments marocaine nécessaire et indispensable.

L'objectif de ce travail était de compléter et de mettre à jour l'ancienne version de la table de composition des aliments disponible au Maroc, afin de fournir des données adéquates et plus fiables sur la composition des aliments utilisés dans notre pays.

#### *6.1.2. Méthodes*

La méthode indirecte de compilation des tables a été utilisée pour compléter les données de cette table de composition des aliments. Elle est basée sur les données existantes et publiées dans la littérature.

La compilation de données de notre table a été effectuée conformément aux normes et aux démarches validées par l'Organisation des Nations Unies pour l'alimentation et l'agriculture (FAO)/ INFOODS [163].

Les données nationales spécifiques à la population Marocaine étaient utilisées comme première source pour compléter les valeurs nutritionnelles de cette table [162,164]. Ensuite, nous avons eu recours aux tables de composition des aliments de la région : la table de composition tunisienne [165] et la table de composition des aliments d'Afrique de l'Ouest [166]. En fin, les tables de composition des aliments de la France (Ciqual 2017) [167], des Etats Unis d'Amérique (USDA 2016) [168], et du Royaume-Uni (McCance et Widdowson/ M&W 2015) [169], ont été utilisées en complément des précédentes.

#### *6.1.3. Principaux résultats*

Cette table de composition des aliments marocaine comprend 587 aliments et 37 composants. Par rapport à la version de El Khayate R (1984), cette table contient plus de 79% nouveaux aliments. Environ 7% des valeurs nutritionnelles incluses dans cette table provenaient de sources des données marocaines et environ 93% des sources internationales (Tables sur la composition des aliments de la Tunisie, de l'Afrique de l'Ouest, de Ciqual 2017, M & W 2015, et d'USDA 2016).

Une copie de cette table est présentée en annexe 1.

#### *6.1.4. Forces et faiblesses de l'étude*

La méthode indirecte de compilation des tables constitue la principale limite de cette étude, et il est donc nécessaire d'être prudent dans l'utilisation de ses valeurs. La méthode indirecte avec une compilation basée sur des valeurs empruntées à d'autres tables peut constituer une source d'erreur suite aux facteurs de variations entre pays. Dans notre situation, l'utilisation de la méthode directe basée sur les analyses chimiques en laboratoire était difficile à mettre en œuvre, en raison du coût très élevé et des ressources humaines et matérielles nécessaires pour sa réalisation. Une autre limite de cette table est le grand nombre de valeurs manquantes.

Toutefois, la compilation de données conformément aux procédures et aux standards internationaux, est un atout pour cette étude. La production de cette table constituera une référence incontournable dans toutes les études nutritionnelles au Maroc en l'absence d'une alternative plus fiable.

#### *6.1.5. Conclusion*

Malgré ses limites, cette édition de la table de composition des aliments marocaine fournit pour la première fois, depuis 1984, des informations pertinentes sur les compositions des principaux aliments consommés au Maroc.

Ce travail est considéré comme une première étape pour la production d'éditions futures qui devraient inclure les analyses chimiques, un grand nombre d'aliments, et un contrôle strict de la qualité des données. Un travail collaboratif entre laboratoires de recherche est nécessaire pour atteindre cet objectif.

### 6.1.6. Article 6

#### **Update of the Moroccan Food Composition Tables: Towards a more reliable tool for nutrition research and prevention.**

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#### **Abstract**

The last food composition table (FCT) for Morocco was published in 1984 and needs to be updated. We aimed to update the Moroccan FCT with data relevant to the current Moroccan population's diet. The approach used was the indirect method based on pre-existing concentration data available in the literature. The primary data sources for compiling this table were local FCTs, and analytical values reported on Moroccan foods. International food composition data were used as an alternative source when National data were not available. This extended FCT includes nutrient information regarding 37 nutrient components for 587 food items, commonly consumed in Morocco. As compared to the previous version, more than 79% are new items. About 7% of nutritional values were derived from

## **Abstract**

Food composition databases provide comprehensive and representative information on nutritional composition of foods. The last revised version of the food composition table for Morocco was published in 1984 and needs to be updated. The aim of the present project was to update the Moroccan food composition table with data relevant to the current Moroccan population's diet. The approach used in this project was the indirect method based on pre-existing concentration data available in the literature. The primary data sources for compiling this table were local food composition tables, and analytical values reported on Moroccan foods. International food composition data were used as an alternative source when National data were not available. This extended food composition table includes nutrient information regarding 37 nutrient components for 587 food items, commonly consumed in Morocco. As compared to the previous version, more than 79% are new items. About 7% of nutritional values were derived from Moroccan data sources and about 93% from international sources (the Tunisian, the West African and the French food composition table (Ciqal Food Composition Database 2016), McCance and Widdowson's tables (M&W 2015), and USDA 2016). This updated food composition table provides, for the first time since 1984, information on relevant food components of the main foods and dishes consumed in Morocco. It is an important tool to foster nutritional research and prevention strategies in Morocco and a first step towards the compilation of a standardized and continuously updated Moroccan food composition table, further completed with more chemical analysis and high-quality compositional data.

## **Key words**

Food composition database; Food composition table; Food consumption; Nutrient data; Nutritional composition; Morocco.

## **1. Introduction**

Food composition databases provide comprehensive and representative information on nutritional composition of foods (Church, 2015; Martinez-Victoria et al., 2015; Haytowitz and Pehrsson, 2018; Finglas et al., 2017). Food composition databases are an important tool for epidemiological research, public health, nutritional education and prevention, therapeutic diets, food safety, agriculture, food labeling and the food industry (Egan et al., 2007; Church, 2009; Bell et al., 2011; Cunningham et al., 2010). Furthermore, the availability and accessibility of food composition data are a prerequisite for analyzing nutrition intakes in food consumption surveys and for investigating the relationship between diet and diseases in epidemiological settings (Elmadfa & Meyer, 2010; Costa et al., 2013; Durazzo et al., 2019). Food composition data are also an essential source of information for developing dietary guidelines for different population groups as well as for food regulations and safety recommendations (Elmadfa & Meyer, 2010; Sammán et al., 2016; Uusitalo et al., 2011).

Food composition databases are available on different supports, either as printed publications, often known as food composition tables or as electronic (online) databases (Williamson, 2005). These databases provide concentration values for energy and nutrients (e.g., protein, fat, carbohydrates, vitamins and minerals, water) and other important food components (e.g., fiber) per 100 grams for each of the listed foods. These values are either original chemical analytical values performed in analytical laboratories, imputed values, borrowed values or calculated values (Williamson, 2005; Marconi et al., 2018; Black et al., 2011).

It is well known that food consumption patterns and types of foods consumed by the populations vary from country to country. Therefore, an accurate assessment of the intake of nutrients and non-nutritive food components in a population depends on the accuracy of the food composition databases available for this population (Sivakumaran et al., 2018; Pennington et al., 2007).

In Morocco, a country experiencing nutritional transition, the food production methods, the types of food consumed, as well as the pattern of the diet have considerably changed in the past years. In addition, the Moroccan population is exposed to a wide variety of messages about the significant impact of diet on the health and nutritional status, leading to an increasing widespread interest in the nutritional content and value of common foods.

Today, there is a scarcity of data regarding the nutrient composition of Moroccan foods. This critical issue increases the difficulty of analysis and interpretation of dietary data. The limited information on nutrient intakes in the Moroccan population and the scarcity of studies investigating the relationship between diet and health might be partly explained by limitations in the availability of food composition databases. Unfortunately, the development of food composition data has been given little research attention in Morocco so far.

The first Moroccan Food composition table titled “Food Composition Table for use in Morocco” was published in 1977, by the Ministry of Agriculture of Morocco (El Khayate, 1984). This table was revised in 1984 by El Khayate R (El Khayate, 1984) to include data on 122 food items (11 food groups) and 20 food components. Although this table incorporate a large number of food items that are commonly used in Morocco, it is still limited and incomplete in terms of food coverage, components, and information needed for researchers. Moreover, this table includes a large number of missing values. Therefore, there is a need to update and to supplement the information available in the Moroccan food composition tables with other recent and reliable sources of food concentration data.

The present work involving Moroccan and International multidisciplinary teams is aimed at producing an update of the Moroccan food Composition table containing data relevant to the Moroccan population and their current eating habits. This food composition table will be a useful reference for health professionals, dietitians, researchers, agriculturalists, food industry professionals, policy-makers, consumers and the general public in our country. This table may also be useful for other neighboring countries with similar food consumption and

habits or for Moroccan immigrant populations in other countries. To the best of our knowledge, this is a first attempt to produce up-to-date and reliable Moroccan food composition data since 1984.

## **2. Methods**

The approach used in this study was the indirect method based on pre-existent data in the literature. Our data were compiled according to international standards and guidelines for food composition data set by the FAO/INFOODS (FAO/INFOODS, 2012).

The data included in our food composition table have been collected from different sources. Our primary source was the revised local food composition table published in 1984, and the analytical values reported on Moroccan foods (El Khayate, 1984). In order to evaluate if information on food composition, from this source is still valid, all values included in this table have been carefully checked, and modifications have been applied when new analytical data were available in the Moroccan published and unpublished literature.

A range of composite dishes and prepared foods were included in this table, predominantly traditional recipes commonly consumed in Morocco. Before resorting to International resources of data, nutrient data of these recipes was derived from local sources or from data published by the Centre d'Information et de Recherche sur les Intolérances et l'Hygiène Alimentaires (CIRIHA) in Brussels (CIRIHA, n.d.) that contained information on the composition of traditional recipes frequently eaten by the Moroccan population living in Belgium.

In order to obtain a more complete list of food items consumed in Morocco, literature searches were carried out using scientific literature, popular Moroccan cookbooks, and unpublished sources. Generally, the table was extended to include a food list representing the most frequently consumed foods in Morocco, which were grouped into 15 food groups. The nutrients included in this food composition table were selected for their importance in the field of nutritional epidemiology (Slimani et al., 2000).

Whenever this primary source of local analytical data was insufficient, values were imputed from similar food items of food composition tables in the region, more in particular the Food composition table of Tunisia (NINT, 2007) and the West African food composition table (2012) (FAO, 2012). Finally, the French food composition table Ciqual 2017 (FAFEOHS,207), the McCance and Widdowson's tables (PHE, 2015), and the United States Department of Agriculture (USDA) Food Composition Database (USDA, 2016) were used to compile our food composition table and to reduce the amount of missing information.

Food names were chosen to describe the food items as appropriately as possible. We used generic names (e.g., egg, bread), and extra specifications/descriptors such as type (e.g., white), processing (e.g., roasted, boiled), physical state (e.g., raw), parts (e.g., seed), when appropriate. Most of the composite dishes are given by their Moroccan names. A unique five digits code was assigned to each food item. The code has been assigned in such a way that the first two digits represent a food group, and the last three digits represent a food item and its



specifications. All food composition values are expressed per 100 g edible portion (EP) of the food (i.e., meat without bone, apple without a core, etc.). The term trace (Tr) in the Table indicates that only a trace of the nutrient in question was known to be present. A zero (0) indicates that the content of the component is considered to be zero.

Quality controls were performed for clusters of nutrients whenever possible (e.g. sum of SFA + MUFA + PUFA is lower than total fat; energy kcal should be comparable to energy calculated from macronutrients, etc.).

### **3. Results**

The present version of the Moroccan food composition table includes information on 37 components for 587 food items of which 465 (79.2%) are new items. Food groups where a large number of items have been added are cereals and their products, meat and poultry and their products, and dairy products. Table 1 shows a comparison between the last FCT (1984) and the currently updated FCT (2019) in terms of a number of components, list of food groups and number of food items in each group.

In this Table, about 7% of nutritional values were derived from Moroccan data sources and about 93% from foreign sources.

Food composition items included in our table are energy (kcal), water (g), total proteins (g), total fats (g), carbohydrates (g), sugars (g), starch (g), dietary fiber (g), saturated fatty acids (g), monounsaturated fatty acids (g), polyunsaturated fatty acids (g), cholesterol (g), sodium (mg), potassium (mg), calcium (mg), magnesium (mg), phosphorus (mg), iron (mg), zinc (mg), copper (mg), manganese (mg), chloride (mg), selenium (mcg), iodine (mcg), vitamin A (mcg), B-carotene (mcg), vitamin D (mcg), vitamin K (mcg), vitamin E (mg), vitamin C (mg), vitamin B1 (mg), vitamin B2 (mg), vitamin B3 (mg), vitamin B5 (mg), vitamin B6 (mg), vitamin B9 (mcg) and vitamin B12 (mcg).

The updated version of the Moroccan food composition table (2019) is given in Excel format as a supplementary material.

### **4. Discussion**

The main objective of this work was to produce an updated version of Moroccan food composition tables containing data relevant to the Moroccan population.

In Morocco, the latest food composition table was published in 1984. To date and to the best of our knowledge, this table has never been updated. The absence of an official department responsible for the generation of an official food composition table as well as a lack of coordination and cooperation between several departments of research and universities may explain, in large part, a delay in the development of an updated food composition table in our country.

In this work, the approach chosen to update our Food Composition Table was the indirect method. Generally, there are three common methods used to compile or update the food composition databases: direct, indirect or a combination of methods (Greenfield & Southgate, 2003; Lopes et al., 2015). The direct method is characterized by analytical measurements of food components, according to well-defined sampling and recognized procedures (Greenfield & Southgate, 2003). Direct analysis of foods is the preferred method to obtain highly reliable data that reflects the true component content in a food. However, this method requires significant financial resources and skilled laboratory investigators and is time-consuming (Marconi et al., 2018; Koréissi-Dembélé et al., 2017). At the moment this direct method is practically difficult to be conducted in Morocco due to lack of resources. Alternatively, food composition tables can be updated by indirect methods or through a combination of methods. The indirect method, which has a much lower cost, consists of using pre-existing data on foods and nutrients of interest, taken from published literature or unpublished laboratory reports (Greenfield & Southgate, 2003). The indirect method is most commonly used when chemical analysis data are limited, and it is considered the best alternative in our Moroccan context. However, this method has less control over the quality of the data, and great care must be taken in their assessment for inclusion in the database. The combined method consists of a combination of the direct and indirect methods, by including original chemical analytical data and values taken from the literature and from other databases as well as imputed and calculated values. This method has been widely used, to elaborate a food composition database, in previous studies (Lopes et al., 2015; Tardío et al.).

Generally, minimization of the number of imputed and calculated values, included in the database, increases the reliability of the food composition data. Therefore, in our context, and in order to increase the quality of our database and to ensure that the nutrient contents of the foods are appropriate for our country, efforts were made to include as many analytical data as possible from Moroccan sources. Unfortunately, our local data was rather incomplete and needed to be extended by additional data. In addition, details of the chemical analysis, sample, and method of preparation were lacking in the most of local sources. Food composition information derived from unreliable sources (e.g. industry) and/or obtained through invalidated laboratory methods may produce misleading information on food composition and as such increase confusion and lead to mistrust of healthy eating messages (Buttriss & Benelam, 2010). Therefore, further completion of the food composition table with other databases (e.g. from neighboring regions/countries) is indispensable.

The Food Composition Table presented in this paper was based, for a large part, on international databases. For example, the Tunisian food composition table was chosen as the preferred starting point for international data collection, because Tunisian foods are considered to be similar to our Moroccan foods, and therefore the Tunisian food composition table contains a wide range of similar foods that are consumed in Morocco. Respecting the standard procedure of selecting first the tables in the region (e.g., neighboring countries) with foods that are closest to the Moroccan foods, the West African food composition table was

selected as our second foreign source. Other international databases were used when no information was found in Moroccan, Tunisian or West African food composition tables. These extra international sources of data (CIQUAL 2017, the M&W 2015 and the USDA 2016) were chosen because they are the most extensive and reliable databases in the world and they are regularly updated. Similar approaches were used by several investigators in the world to complete their food composition databases (Gnagnarella et al., 2004; Shai et al., 2003; Machackova et al., 2010; Merchant et al., 2005; University of Helsinki, 2011; University of Dhaka, 2013; Arab Center for Nutrition, 2011). However, this approach has several disadvantages, and the quality of data should be taken with caution. For instance, the nutrient content of food items included in the international databases may differ from those grown in our country as a result of differences in the content of nutrients and other substances in the soil, differences in exposure to the sun, weather conditions, agricultural practices, and for different varieties of plants and animals (Marconi et al., 2018; Lupiañez-Barbero et al., 2018).

In addition, food component variability from country to country and errors in matching similar foods or in the identification of the exact correspondence dish on other sources may lead to over or under estimation of nutrients (Puwastien, 2002). Also, differences in fortification guidelines between countries may be reflected in the food composition database, as such necessitating caution when borrowing food composition values from other countries. Therefore, in order to evaluate the coherence and validity of our data, particular attention should be directed to comparable analysis of nutrient composition in further researches.

Some nutrient values borrowed from Tunisian FCT were estimated by recipe calculations. This approach leads to an approximation of the real nutrient composition (Machackova et al., 2018). However, there are differences between calculated and direct chemical analyses values, due to different types of cooking equipment, the surface area of food contact exposure, length and temperature of cooking, and volume of product on the yield factors, retention factors, and water/fat, loss/gain factors (Rand, 1991); Parpinel et al., 2000; Reinivuo et al., 2009). This limitation may be a source of some errors in nutrient estimation.

One other limitation in this table is the existence of some missing values. The assignment of zeros to these missing values in the analyses leads to underestimation of daily nutrient intakes. The impact of missing values on the underestimation depends on its proportion and on the frequency of consumption of foods with incomplete data (Charrondiere et al., 2002). However, the number of missing values in our table is very small compared with the last version and gives an enormous amount of additional information.

An important strength of this updated Moroccan food composition table is the standard operating procedures that were strictly followed and the important contribution of world leaders in this area of compiling national food composition tables. The large amount of food components included as well as the exhaustive list of foods and dishes are two important features that contribute to the usefulness and quality assurance of this updated food composition table.

## 5. Conclusion

The Food Composition Table presented in the paper provides, for the first time since 1984, information on relevant food components of the main food items consumed in Morocco. Despite some limitations, it is a useful tool for assessing Moroccan' nutrient intakes, accessible to the public, and it should be continuously updated. Finally, we hope that this work will be considered as a first step for producing future releases with more chemical analysis, a high number of food items, and high-quality composition data. Indeed, more research and more collaborative work are necessary to achieve this objective.

## Conflicts of Interest

The authors declare that they have no competing interests.

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## Supplementary Material

The updated version of the Moroccan food composition table- 2019 (Excel format).

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**Table 1. Nutrient composition, list of food groups and number of food items in each group present in the last FCT (1984) and the current updated FCT (2019).**

	The FCT (1984)	The updated FCT (2019)	Differences/ increasing in n (%)
<b>Components</b>	<b>20</b>	<b>37</b>	17 (45.9)
<b>Food groups</b>	<b>11</b>	<b>15</b>	4 (26.6)
Cereals and their products	28	109	81 (74.3)
Starchy roots, tubers and their products	-	13	13 (100)
Nuts, seeds and their products	-	37	37 (100)
Vegetables and their products	16	39	23 (58.9)
Legumes and their products	5	12	7 (58.3)
Fruits and their products	16	29	13 (44.8)
Condiments and sauces	-	25	25 (100)
Fat and oils	2	12	10 (83.3)
Dairy products	8	45	37 (82.2)
Eggs and their products	1	5	4 (80.0)
Sugars, sweeteners and syrup	3	18	15 (83.3)
Beverages (alcoholic and nonalcoholic)	23	81	58 (71.6)
Meat and poultry and their products	4	104	100 (96.1)
Fish and their products	16	31	15 (48.3)
Prepared foods	-	27	27 (100)
<b>Total food items</b>	<b>122</b>	<b>587</b>	<b>465 (79.2)</b>

## **6.2. Adaptation et validation de questionnaire de fréquence alimentaire (FFQ) dans la population marocaine**

Les questionnaires de fréquence alimentaires ou Food Frequency Questionnaires permettent d'évaluer la consommation habituelle de certains aliments. Ils sont largement utilisés pour tester les associations entre les habitudes alimentaires et la survenue de plusieurs maladies incluant le cancer. Par ailleurs, l'administration de ces questionnaires alimentaires dans une population donnée nécessite une validation préalable.

Parmi les travaux réalisés dans le cadre de cette thèse, nous avons fait partie de l'équipe ayant adapté et validé le FFQ pour le contexte marocain.

Notre étude de validation a montré une validité du questionnaire FFQ satisfaisante [82], les coefficients de corrélation variaient entre 0,24 pour les fibres et 0,93 pour les acides gras mono-insaturés. Cette étude reporte aussi une reproductibilité du questionnaire satisfaisante, les coefficients de corrélation s'échelonnaient de 0,69 pour les matières grasses et 0,84 pour la vitamine A.

Ainsi, Il peut être utilisé comme un instrument fiable pour évaluer les apports alimentaires chez l'adulte au Maroc.

## Chapitre IV : Conclusion générale et perspectives

### 1. Synthèse des résultats

Notre travail a tout d'abord permis de faire le point des connaissances sur les taux d'incidence et de mortalité liée au cancer du sein au Maroc, et de faire une comparaison avec ceux issus d'autres pays à faibles et moyens revenus et des pays développés. Nous avons montré que les taux d'incidence du cancer du sein au Maroc sont relativement bas par rapport à ceux observés dans certains pays développés, mais ces taux ont considérablement augmenté pendant ces dernières décennies. Pour la mortalité, les taux observés au Maroc en 2012 étaient presque similaires à ceux rapportés dans certains pays de la région, mais légèrement plus élevé que le taux moyen de mortalité par ce cancer pour la population mondiale.

Concernant les facteurs de risque de cancer du sein dans notre population, les résultats de notre première étude ont montré que le fait d'avoir les premières règles à un âge inférieur ou égal à 13 ans était associé à un risque significativement augmenté de survenue d'un cancer du sein. Ses résultats ont montré également que les femmes nullipares avaient un risque plus élevé du cancer du sein, en comparaison avec celles qui ont eu au moins un enfant. En revanche, les femmes ayant eu leur première grossesse à terme avant 20 ans étaient moins à risque d'avoir un cancer du sein comparativement aux autres femmes ayant eu leur première grossesse après 20 ans.

Dans notre deuxième étude nous avons montré que le fait d'avoir un score de mode de vie sain élevé, caractérisé par une alimentation saine, une activité physique élevée, un faible IMC, une absence de consommation d'alcool et de tabac, et une durée prolongée de l'allaitement, était significativement associé à une diminution de risque de cancer du sein chez les femmes de notre population.

Cette étude a permis également de décrire les associations entre certains facteurs anthropométriques et le risque de cancer du sein. Elle a montré que les indicateurs d'obésité abdominale étaient positivement associés au risque de cancer du sein. Un tour de taille et un tour de hanches élevés étaient significativement associés à l'augmentation de risque de cancer du sein chez les femmes en pré- et en postménopause. Les analyses sur les silhouettes ont montré qu'une large silhouette à l'enfance était associée à une diminution significative de risque de cancer du sein chez les femmes en préménopause et à la limite de la signification statistique chez les femmes en postménopause. En revanche, les femmes ayant une forte évolution de trajectoire de la silhouette avaient un risque élevé de cancer du sein en pré- et en postménopause, comparativement aux femmes ayant une stable ou faible évolution de cette trajectoire.

Cette étude a permis également d'identifier certaines professions et secteurs d'activité associés à un risque élevé de cancer du sein chez les femmes de notre population. Les femmes ayant travaillé dans certaines professions du secteur de l'agriculture en particulier celles employées comme ouvrière agricole avaient un risque élevé de cancer du sein, comparativement aux femmes n'ayant jamais travaillé dans cette profession. Les analyses

stratifiées sur la durée d'emploi dans cette profession (< 10 ans, ≥10 ans) ont montré une élévation de risque de cancer du sein avec l'augmentation de la durée de l'emploi.

Ce travail de thèse a également permis de préparer et de valider un outil indispensable pour l'analyse des données nutritionnelles dans notre contexte, il s'agit de la table de composition des aliments marocaine. Nous avons complété et mis à jour l'ancienne table de composition des aliments marocaine, ainsi, nous avons fourni pour la première fois, depuis 1984, des informations sur les compositions des principaux aliments consommés au Maroc.

## **2. Perspectives de recherche**

Ce travail de thèse a permis de mieux comprendre le rôle de certains facteurs de risque reconnus et suspectés dans la survenue de cancer du sein chez les femmes marocaines de la région de Fès. Cependant, notre travail a soulevé un certain nombre de questions et pistes de recherche pour lesquelles il serait intéressant de mener des études complémentaires et approfondies à l'avenir.

Dans un premier temps, nous envisageons de poursuivre nos analyses et d'explorer les associations entre d'autres facteurs de risque et le cancer du sein dans notre population en particulier les facteurs nutritionnels. Les analyses d'association entre les profils alimentaires des femmes et le cancer du sein seront effectuées à l'aide de deux approches méthodologiques dites "méthode à priori" et "méthode à posteriori". La méthode à priori nous permettra d'évaluer l'adhésion des femmes aux recommandations nutritionnelles ou à des régimes référentiels prédéfinis dans la littérature, tels que le Mediterranean Diet Score, le Diet Quality Index, et le Healthy Eating Index etc. La méthode à posteriori reposera sur les données alimentaires recueillies auprès des femmes de notre étude pour caractériser des profils alimentaires, en utilisant des techniques statistiques spécifiques (analyse en composantes principales, analyse factorielle...).

Dans le cadre de ce travail de thèse nous avons participé au développement et à la mise en place d'une étude multicentrique sur le cancer du sein au Maroc "EDSMAR Study" (<http://edsmar.iarc.fr/>) (décrit brièvement en Annexe II), dont le recrutement est actuellement en cours. L'EDSMAR Study est menée en partenariat avec le CIRC, l'Institut de Recherche sur le Cancer de Fès (IRC) et l'Institut National d'Oncologie de Rabat (INO). Dans cette étude il est prévu d'exploiter les données recueillies sur les facteurs de risque de cancer du sein dans le centre de Fès et de Rabat. Ainsi, elle permettra de compléter et de confirmer les résultats présentés dans ce travail de thèse, et d'apporter des éléments de réponse sur certaines questions que nous avons soulevées précédemment. Il est important également de signaler que dans le cadre de l'EDSMAR Study, une collecte d'échantillons biologiques et biopsies de tumeurs est effectuée, cela permettra de mieux comprendre les caractéristiques des sous-types moléculaires de cancer du sein chez les femmes marocaines ainsi que leurs facteurs de risque associés.

Etant donné que les questionnaires utilisés pour le recueil d'informations sur les facteurs de risque de cancer du sein pour l'étude BreCaFez Study et l'étude EDSMAR Study sont presque identiques, nous envisageons d'effectuer des analyses poolées regroupant les données de ces

deux études. Ces analyses permettront d'avoir un effectif important de femmes et de palier au problème de puissance statistique.

Notre étude qui porte sur le lien entre le mode de vie sain et le cancer du sein a montré une différence de risque importante entre les cas et les témoins. Il apparaît par ailleurs, nécessaire de réaliser d'autres études avec l'objectif d'évaluer le niveau de connaissance des femmes marocaines sur un mode de vie sain et sur les facteurs de risque de cancer du sein.

Le travail réalisé sur le rôle de la profession et le secteur d'activité dans la survenue du cancer du sein dans notre population ouvre également diverses perspectives. Il est potentiellement important de réaliser des études plus approfondies avec des méthodes d'évaluation de l'exposition professionnelle détaillées pour mieux élucider l'impact des expositions professionnelles sur le cancer du sein chez certaines catégories professionnelles en particulier dans le secteur de l'agriculture.

Etant donné que l'association entre l'anthropométrie et le risque du cancer du sein varient à travers les différentes périodes de vie de la femme, il serait approprié de mener des études longitudinales de la naissance à l'âge adulte chez les femmes marocaines. Ces études permettraient de mieux comprendre les mécanismes impliqués dans l'association entre l'anthropométrie et le risque de cancer du sein dans notre contexte marocain.

D'après les observations relevées de nos études concernant la différence entre les statuts socio-économiques des cas et des témoins, un autre axe de recherche intéressant pourrait être l'étude de l'influence des facteurs socio-économiques et géographiques sur la survenue de risque de cancer du sein chez les femmes marocaines.

Notre travail concernant la mise à jour de la table de composition des aliments marocaine peut-être un point de départ pour d'autres recherches visant à fournir des données plus fiables sur les compositions des aliments consommés au Maroc, particulièrement celles basées sur les analyses chimiques.

### **3. Point de vue santé publique**

Au Maroc, le cancer du sein constitue un véritable problème de santé publique de par sa morbidité, sa mortalité et son coût généré pour la société. L'amélioration de sa prévention est potentiellement importante pour la réduction de nombre de nouveaux cas de ce cancer dans notre pays.

Un Plan National de Prévention et de Contrôle du Cancer (2010-2019) a été lancé en 2010, par la Fondation Lalla Salma - Prévention et traitement des cancers et le ministère de la Santé du Maroc. Ce plan a retenu parmi ses priorités la prévention, le dépistage et le traitement des cancers du sein et du col de l'utérus au Maroc. L'un des axes stratégiques de ce plan est la promotion des activités de prévention et de détection précoce de cancer du sein. Les résultats présentés dans ce travail thèse peuvent constituer un support très utile pour l'élaboration de stratégies de prévention et de lutte contre le cancer du sein pour les futures éditions de ce plan.

Les résultats de nos études ont permis d'identifier plusieurs facteurs de risque de cancer du sein qui sont modifiables et accessibles à la prévention primaire. Toutefois, il est nécessaire d'instaurer des mesures d'information et de sensibilisation efficaces, dans le but d'induire un changement des facteurs modifiables identifiés dans notre population. Par ailleurs, il serait pertinent que les messages de santé publique, destinés à la prévention primaire de cancer du sein dans notre pays, encouragent les femmes marocaines à adopter des comportements protectifs dans leur vie reproductive (ex. allaitement maternel prolongé, parité...) ainsi que dans leur mode de vie (ex. alimentation saine, activité physique élevée, faible IMC, absence d'obésité abdominal...).

Par ailleurs, le Maroc a fait des efforts importants pour assurer l'accès de la population aux services de dépistage et de diagnostic du cancer du sein à travers le programme national de détection précoce de cancer du sein généralisé dans les 12 régions du royaume en 2010. Ce programme cible les femmes âgées de 40 ans à 69 ans et les femmes ayant un antécédent familial de cancer du sein. En 2016, 1,5 million de femmes ont participé à ce programme [170].

Les résultats de notre travail peuvent servir à orienter les mesures de prévention secondaire de cancer du sein dans notre pays. Ainsi, les activités de programme national de détection précoce de cancer du sein au Maroc peuvent cibler les femmes à risque élevé en tant que population prioritaire. De plus, les groupes de femmes à haut risque pourraient être suivis régulièrement et bénéficier d'une surveillance particulière de leur état de santé.

Enfin, pour améliorer les activités de prévention du cancer du sein considérées comme une approche de santé publique prometteuse pour réduire la morbidité et la mortalité liées à ce cancer dans notre pays, il est potentiellement important de renforcer les collaborations multisectorielles et multi-acteurs impliquant les différents composition de la société marocaines, y compris les Organisations Non Gouvernementales (ONG) actives en matière de sensibilisation et de la lutte contre le cancer.

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# Annexe I : Table de composition des aliments marocaine

Food code	Source	Water (g)	Prot (g)	Fat (g)	CHO (g)	E (kcal)	Sug (g)	Sta (g)	Fib (g)	SFA (g)	MUF A (g)	PUFA (g)	Chol (mg)	Vit A (mcg)	BetaC (mcg)	Vit D (mcg)	Vit E (mg)	Vit K (mcg)	Vit C (mg)	Vit B1 (mg)	Vit B2 (mg)	Vit B3 (mg)	Vit B5 (mg)	Vit B6 (mg)	Vit B9 (mcg)	Vit B12 (mcg)	Na (mg)	K (mg)	Ca (mg)	Mg (mg)	P (mg)	Fe (mg)	Cu (mg)	Zn (mg)	Chlor (mg)	Mn (mg)	Se (mcg)	I (mcg)			
01.00 1	Ciqual	10.7	9.83	1.97	61	334	0.89	53.8	15	0.25	0.22	0.96	0	0	7	0	1	5.9	0	0.34	0.21	2.99	1.4	0.29	47	0	2.9	469	26.4	104	346	3.32	0.34	2.78	60	3.14	1.5	2.7			
01.00 2	M1/Ciqual	8.22	16.9	6.9	55.7	378	1.2	52.6	10.6	1.22	2.18	2.54	0	0	ND	0	1.09	ND	0	0.76	0.14	0.96	1.35	0.12	56	0	2	429	54	177	523	4.72	0.63	3.97	70	4.92	9	ND			
01.00 3	Ciqual/USDA	13.3	13.2	6.07	58.1	358	0.87	52.2	7	0.71	1.61	3.29	0	0	8	0	2.44	0	ND	0.36	0.32	1.52	0.77	0.49	184	0	5	563	47	197	457	4.57	0.59	3.1	ND	2.03	ND	ND			
01.00 4	M1/Ciqual	10.33	12.1	2.85	78.4	397	3.17	59.2	11	0.37	0.29	0.95	0	0	0	0	1.4	30	0	0.38	0.12	6.17	1.02	0.39	32	0	9.05	479.57	36.51	124.4	333.8	4.7	0.35	4.49	ND	3.31	189.1	8	2.7		
01.00 5	M1/Ciqual/USDA	10.15	11.5	2.81	79.4	398	3.3	62.5	1.7	0.6	0.29	1.59	0	0	0	0	1.44	1.9	0	0.40	0.14	5.4	0.85	0.27	41	0	14.18	445.26	46.79	123.8	357.6	4.47	0.43	4.45	ND	3.406	ND	ND			
01.00 6	WA	13.1	12.6	1.54	65.6	327	0	12.2	0.2	0.27	0.2	0.63	0	0.9	5	0	1.01	1.9	0	0.38	0.12	5.46	0.95	0.3	45	0	2	363	29	126	288	3.19	0.43	2.65	ND	3.99	70.7	0.6			
01.00 7	WA/MW	9.3	32	17	27.6	410	5.5	4.8	9.3	2.3	3.5	9.1	0	0	13	0	0.72	ND	Tr	0.7	0.28	2	0.18	0.82	375	0	5	1740	232	245	468	7.8	1.48	4.73	7	2.6	14	6			
01.00 8	M1/T/Ciqual/USDA	8.4	9.42	3.9	77.4	386.2	1.6	64.1	7.3	0.67	1.25	2.16	0	22	97	ND	0.49	0.3	0	0.39	0.2	3.63	0.42	0.62	19	0	0.57	334.26	14.92	110.4	229.3	3.33	0.27	4.26	50	0.49	15.5	ND			
01.00 9	M1/MW/Ciqual/MW	12.89	8.45	1.9	78	371.7	0.16	77.8	1.18	0.16	0.18	0.16	0	0	0	0	0.09	0.1	0	0.07	0.05	1.6	1.34	0.15	20	0	5.04	276.5	19.28	35	108	0.8	0.11	1.16	10	1.1	15	13.8			
01.01 0	WA/MW	11.9	6.7	2.2	81.3	357	1.3	80	3	0.7	0.7	1	0	0	0	0	0.6	0.82	0	0.38	0.07	5	ND	0.51	40	0	6	249	22	143	277	1.9	0.28	2.02	230	2.3	10	ND			
01.01 1	WA/Ciqual	11.4	6.3	0.3	81.4	354	0	58.4	0.2	ND	ND	ND	ND	0	0	0	0.7	ND	0	0.06	0.1	2	1.1	0.06	15	0	11	194	22	130	98	1.7	<1	2.1	ND	2	<5	<10			
01.01 2	T/WA/Ciqual/USDA	9.2	10.5	3.3	66.0	339	2.48	62.9	10	0.46	0.99	1.37	0	0	0	0	0.07	6.4	0	0.24	0.14	2.93	0.539	0.25	29	0	6	350	28	311	287	4.4	0.38	0.27	60	1.258	12.2	ND			
01.01 3	WA	9.4	9.3	3.9	65.5	354	0	0	9.9	ND	ND	ND	ND	0	0	0	1.1	ND	0	0.36	0.17	3.4	ND	0.25	30	0	14	298	24	311	249	3.9	0.18	2.08	ND	ND	ND	ND			
01.01 4	M1/T/Ciqual	13.9	5	2.1	56.2	394.7	0.8	52.2	15.6	0.24	0.15	0.56	0	2	13	0	0.02	2.2	0	0.19	0.11	4.6	0.28	0.26	19	0	328.95	539	32.67	127	247.5	1.07	0.045	2.6	110	1.32	37.7	ND			
01.01 5	M2	46.2	5.9	5.9	1.7	76	1.6	0	3.1	0.8	3.1	1.2	0	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND		
01.01 6	M2	66.5	5.4	1.7	5	53	5	0	1.3	0.9	0.3	0	3.7	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND		
01.01 7	M1/T/USDA	12.67	12.6	1.05	72.8	360	0	0	3.63	0.15	0.12	0.43	0	0	0	0	0.26	ND	0	0.28	0.08	3.31	0.58	0.1	72	0	1	186	29.95	47	288.1	7.07	0.034	2.6	ND	0.619	ND	ND			
01.01 8	Ciqual	12.1	10.9	1.25	71.4	352	1	0	3.37	0.21	0.14	0.52	0	0	ND	0	0.1	30	0	0.25	0.063	2.16	0.54	0.094	57	0	1.2	152	16.9	26.5	102	0.92	0.3	2.18	ND	2.31	1	0.3			
01.01 9	Ciqual	12.6	7.88	1.8	74	350	0	68	3.2	ND	ND	ND	ND	0	<50	ND	<1	ND	ND	0.07	0.06	<0.05	0.39	0.08	35	ND	1.7	144	1.55	35	104	<1	ND	<1	94	<1	<5	<10			
01.02 0	M1/T/USDA	10.13	13.4	1.5	73.9	376	0	2.7	0.35	0.24	0.85	0	26.16	8	156.9	8	0	0.26	ND	0.32	0.29	0.1	3.89	1.24	0.11	20	0	9.56	243.34	37.27	44	330.1	2.82	1.03	2.62	ND	0.78	ND	ND		
01.02 1	M1/Ciqual	59	5.19	0.64	33.2	165	0.1	28.7	1.6	0.02	0.022	0.064	0	0	0	0	<0.08	<0.08	0	0.09	0.03	0.2	0.27	0.094	15	0	<5	120	22.5	24	260.6	1.83	0.056	0.57	29.1	0.46	<20	<20			
01.02 2	M2	66.9	4.1	2.8	22.7	132	2.4	20.3	1.8	0.5	1.2	0.7	0.8	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND		
01.02 3	M2	66.2	6.5	4	20	142	2.1	17.9	1.6	1.2	1.7	0.7	6.9	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	
01.02 4	M2	65	6.3	5.1	19.9	151	7	12.9	1.8	1.2	2.2	1.3	1.2	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	
01.02 5	M2	65.7	3.4	4.6	22.7	146	8	14.7	2	0.9	2.2	1.2	1.3	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	
01.02 6	M2	78	4.7	0.6	14.7	82	3.4	11.2	0.3	0.3	0.1	0.1	1	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	
01.02 7	M2	45	7	6.7	38.5	242	7.7	30.7	1.4	2.2	2.9	1.1	6.6	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	
01.02 8	M2	71.3	2.9	3.1	22.3	129	5.6	16.8	0.8	0.5	1.7	0.7	0	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
01.02 9	M2	72.3	2.9	5	19.8	136	13.1	6.6	0.2	3.1	1.2	0.2	13.1	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
01.03 0	M2	84.1	3.4	1.4	11	70	5.2	5.7	0.2	0.8	0.3	0.1	3.5	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
01.03 1	Ciqual/MW	30	7.05	3.45	57.5	290	3.3	54.1	2.2	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	0	0.41	0.03	1.7	ND	0.03	8	ND	630	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	
01.03 2	M2	75.5	6.4	2	8.8	78	0.5	8.3	3.9	0.3	0.9	0.6	0	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
01.03 3	T/MW/USDA	10.25	12.7	1.58	74.6	371	71.4	0.8	2.4	0.23	0.19	0.65	0	0	0	0	0.11	0.21	0	0.09	0.06	1.7	0.43	0.11	23	0	7	162	25	48	190	2.1	0.32	1.5	25	0.69	62.2	Tr			
01.03 4	WA/MW	9.5	12	1.5	75.8	359	2.2	73.6	3.7	0.3	0.1	0.8	0	0	0	0	0.11	ND	0	0.16	0.03	1.2	0.3	0.13	17	0	4	216	23	53	182	1.2	0.29	1.41	20	0.9	20	Tr			
01.03 5	MW	10.5	13.4	2.5	66.2	324	3.7	62.5	ND	0.4	0.3																														

01.04 0	Cqual	6.12	13.9	20.9	28.1	398	0.9	0	21	4.17	7.55	7.46	0	0	0	0	0	0	4.92	1.9	0	2.75	0.28	34	7.39	4.07	63	0	5	1490	57	781	1680	18.5	0.73	6.04	ND	14.2	15.6	ND			
01.04 1	Cqual/MW	9.9	7.24	1.12	70.9	344	1.59	65.8	9.5	0.22	0.19	0.7	0	0	0	1.01	ND	<0.5	0.4	0.22	1	1	0.35	78	1	0.35	78	0	3.63	356	23.8	64.6	216	1.8	0.3	1.9	ND	1.8	2.5	ND			
01.04 2	M1/T/Cqual/MW	12	11	1.2	74.7	364	1.5	0	4.18	0.2	0.1	0.6	0	0	0	0.3	ND	0	0.18	0.06	1.3	ND	0.15	22	0	0.15	22	0	2	150	26.5	20	350	3.5	0.21	2.9	ND	0.6	2	10			
01.04 3	T/Cqual	6.88	9.91	4	76	380	60	0	16	0.43	0.23	1.07	0	0	0	0.41	2.2	0	0.24	0.14	3.2	0.15	0.36	8	0	0.15	0.36	8	0	0	500	0	92.5	298	2.88	0.45	2.4	ND	1.32	1	5		
01.04 4	Cqual/MW	5.13	35.8	21.4	22.9	460	7.5	0	10	3.04	4.98	12.1	0	0	72	0	11.5	135	0	0.67	0.74	1.7	0.52	573	0	0.52	573	0	7.5	2230	178	335	527	5.19	2.26	4.46	110	2.29	11	0.5			
01.04 5	Cqual	11.4	6.87	2.5	73.9	357	0.9	70	3.3	0.46	0.97	0.92	0	0	<	0.25	0.66	1.78	<0.5	0.33	<	0.01	0.13	25.1	0	0.13	25.1	0	<5	270	9.5	110	300	0.79	0.18	1.4	29.2	2.3	<20	<20			
01.04 6	Cqual/MW	10.5	6.23	2.1	78.1	361	0.64	0	2.55	0.27	0.48	0.94	0	0	97	0	0.63	0.3	0	0.2	0.084	4.18	0.052	34	0	0.21	34	0	1	105	4	32.5	79.5	1.01	0.14	0.44	71	0.056	3.2	0.6			
01.04 7	Cqual/MW	10.3	22.4	6.69	47	359	2.6	43.8	10.8	0.69	1.5	2.98	0	0	25	0	0.83	9.1	0	0.49	0.11	1.76	0.61	0.49	437	0	0.49	437	0	64	846	45	166	318	4.86	0.91	2.81	60	1.6	2	ND		
01.04 8	T/USDA	8.32	0.26	0.05	91.2	90.3	7	0	0.9	0.01	0.02	0.03	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	9	3	3	13	0.47	0.05	0.06	ND	0.05	2.8	ND				
01.04 9	MW	3	7.9	0.9	89.6	376	8.2	81.4	3	0.2	0.2	0.4	0	0	0	0.4	0.06	0	1.2	1.3	15	0.3	1.7	333	0.9	1.7	333	0.9	1000	90	5	10	50	7.9	0.03	0.2	1540	0.1	5	10			
01.05 0	M1/T/Cqual/MW	37.7	9.4	2.5	46.4	250	2.8	39.3	4.91	0.81	1.52	0.92	0	0	0	0.34	2.2	0.3	0.41	0.34	4.37	0.51	0.33	40	0.07	0.33	40	0.07	487	204	41.97	53	348.9	1.63	0.93	2.59	800	1.49	29.5	Tr			
01.05 1	M1/T/Cqual/MW	34.3	8.8	1.1	59.1	286	2.86	51.5	3.49	0.64	1.22	0.69	0	0	0	0.3	1	0	0.52	0.33	4.75	0.39	0.04	29	0	0.04	29	0	609	113	22.8	27	259.6	1.58	0.06	0.63	974	0.51	31.5	5.42			
01.05 2	M2/T	36.7	7.1	5	49.4	272	0.9	48.4	1.4	1.8	1.2	1.4	5.5	0	0	0.99	9.65	0	0.14	0.04	1.38	0.17	0.03	21.6	0	0.03	21.6	0	590.9	55.8	9.9	14.1	74.4	0.7	0.06	0.32	ND	0.19	0	68			
01.05 3	Cqual/MW	36	5.58	1.24	46.3	239	1.9	36	8.9	0.2	0.26	0.37	0	0	<50	0	<0.1	ND	0.4	0.29	0.05	2.3	0.5	0.09	24	0	0.5	0.09	24	0	530	179	22.8	29.6	169	1.2	0.19	<1	1050	<1	<5	<10	
01.05 4	Cqual	3.65	9.76	6.16	74	403	5.28	66.7	4.34	2.49	1.99	0.86	Tr	ND	ND	ND	ND	ND	ND	ND	ND	0.11	0.05	28	0	0.11	0.05	28	0	616	175	29.3	33.8	135	1.9	0.18	ND	ND	0.7	2	4		
01.05 5	Cqual	30.9	7.66	1.1	55.9	272	2.3	48.3	2.6	0.22	0.38	0.14	3	9	6	Tr	0.4	ND	0.1	0.1	0.8	0.4	0.17	39	0.1	0.17	39	0.1	619	148	22	29	118	0.9	ND	ND	ND	ND	ND	ND			
01.05 6	Cqual/MW	32.9	8.89	5.75	48.8	285	2.2	46.6	4.75	0.55	1.3	1.1	0	ND	0	Tr	ND	0	0.23	0.1	1.5	0.3	0.06	48	Tr	0.06	48	Tr	550	110	130	31	150	2.3	0.13	0.7	890	0.5	9	19			
01.05 7	Cqual	34.1	7.53	0.92	53	259	2.18	48	2.68	0.17	0	0	ND	ND	<50	ND	<0.1	ND	0.11	0.08	2.6	0.49	0.05	21	ND	0.05	21	ND	543	134	52.7	18.1	84	1	ND	<1	982	<1	<5	<10			
01.05 8	M2	36.8	7	4.5	49.9	269	14.1	35.7	1.5	1.7	1.2	1.1	5.7	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	
01.05 9	M2	37.5	6.5	11.8	41.2	297	1.8	39.4	1.2	3	3.5	4.6	6.5	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
01.06 0	Cqual	10.8	8.97	21.2	54.9	453	49.8	5.05	2.9	4.46	12.3	3.39	19.3	0	80	ND	5.2	ND	2.1	<	1.6	1.3	<	0.13	<	0.13	<	65.5	290	81	79.1	111	1.5	0.3	0.9	73	0.5	ND	2	ND	2		
01.06 1	Cqual	25.8	5.11	9	55.9	333	18.7	26	2.8	4.1	2.94	0.89	43	36	<50	<0.2	0.97	ND	0	0.07	0.18	<	0.05	0.08	132	0.54	0.08	132	0.54	280	278	32.1	18.6	100	0.77	<1	<1	0.5	<1	9.7	<10		
01.06 2	M2/T	36	8.1	2.1	52	260	3.4	48.6	2.7	0.5	0.4	0.8	1	0	0	1.07	9.65	0	0.39	0.1	2.54	0.35	0.11	54.3	0.28	0.11	54.3	0.28	592.45	141.21	12.05	31.9	81.6	0.87	0.11	0.77	ND	0.37	0	68			
01.06 3	Cqual	16.8	8.49	21.5	49.3	438	8.6	40.7	5.3	11	5.67	1.14	58	44	<50	<0.2	1.2	ND	0	0.07	0.13	0.46	0.57	0.17	46	0.82	0.17	46	0.82	456	171	37.1	20.3	114	1.1	0.11	<1	791	<1	<5	<10		
01.06 4	T	36.67	7.94	2.4	46.0	233	36	0	9.6	0	0	0	ND	0	0	ND	ND	0	0.37	0.13	2.48	0	0.05	11.1	0.28	0.05	11.1	0.28	591.85	329.61	1.85	3.7	ND	1.86	ND	0.14	ND	ND	88				
01.06 5	Cqual	33.8	2.62	3.3	51.8	261	4.9	41.1	6.5	1.24	0.98	0.82	4.53	ND	7.6	ND	0.98	<0.8	38.6	0.04	0.02	0.15	0.4	0.025	10.7	0.04	0.025	10.7	0.04	624	75	60	16	95	0.5	0.06	0.36	778	0.19	<20	<20		
01.06 6	M2	37.4	8.1	1.5	44.9	226	2.1	42.8	8.3	0.2	0.1	0.6	0	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	
01.06 7	Cqual	13	6.22	26.2	50	467	35	7.5	3.33	8.21	10.3	3.39	16.5	12.5	0	0.2	0.15	6.5	5.3	0.19	0.21	1.35	0.55	0.038	9.5	0.17	0.55	0.038	9.5	0.17	226	144	60.3	39.3	124	2.2	0.33	0.79	ND	0.32	<2.2	12	
01.06 8	M1/T/Cqual	23.2	8.2	19.1	45.8	406	5.7	32.2	2.6	11.6	5.53	1.09	67	187	135	0.15	0.43	3.22	0.2	0.39	0.24	2.19	0.86	0.06	33.5	0.16	0.06	33.5	0.16	744	118	16.09	16	303.1	0.46	0.22	0.28	694	0.33	22.7	<20		
01.06 9	Cqual	24.7	8.16	14.6	48.3	363	14.1	34.3	2.88	6.69	5.01	1.97	22	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	2.25	ND	0.9	ND	ND	ND	ND	ND	ND	ND
01.07 0	M2/MW	35.5	6	7.5	48.3	290	0.9	47.3	1.4	1.2	2.2	3.6	0	44	12	0.2	0.37	ND	1	0.07	0.18	0.4	0.56	0.07	11	0.8	0.46	152	118	13	111	0.78	0.06	0.6	96	0.15	2	28					
01.07 1	M2/Cal	22.8	10.9	25.6	34.5	412	8.4	26.1	5.9	3.2	15.2	5.7	20.8	1.746	ND	0.02	0.72	ND	3.98	0.01	0.001	0.006	0.006	7	0.9	0	1.766.4	2	224.44	79.89	44.07	93.57	1.5	0.18	0.56	2756.4	1.65	8.15	4.49				
01.07 2	M2/Cal	48.3	7.3	1	40.2	199	2.8	37.4	1.5	0.3	0.2	0.3	1.1	ND	ND	0.14	0.57	ND	0	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	2.01
01.07 3	M2/Cal	49.4	7.8	2	37.7	200	2.7	35.1	1.4	0.6	0.5	0.5	21.2	ND	ND	0.27	0.66	ND	0	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	4.23	
01.07 4	M2/MW	29.1	6.1	22.8	40	392	1.3	38.7	1.4	3.5	7.2	11	0	ND	ND	ND	4.18	ND	0	0.22	0.07	1.2	ND	0.02	19	Tr	0.02	19	Tr	230	87	76	21	81	1.2	0.14	0.6	360	0.3	ND	17		
01.07 5	M2/MW	37.5	5.7	18.7	35.2	338	1.1	34.1	1.3	3	5.9	8.6	32.6	ND	ND	ND	Tr	ND	ND	0.22	0.07	1.3	ND	0.03	21	Tr	0.03	21	Tr	180	110	72	19	71	1.2	0.09	0.5	290	0.3	ND	15		
01.07 6	Cqual	29.2	6.65	20	40.4	375	8.83	31.6	2.32	11.6	4.75	1.83	26.5	ND	70	1.5	1.1	ND	0	0.13	0.11	ND	ND	0.051	56	0	450	172	33.6	22.4	91	0.8	0.075	0.53	ND	0.34	<10	5.9	<10	<10			
01.07 7	M2/Cal	15.2	6.1	29.6</																																							



02.01	WA/CQual/MW	83.3	4.6	0.2	12.2	62.8	6.11	6.14	2.4	0.04	0.002	0.077	0	10500	5560	0	1.01	2.2	5	0.09	0.21	0.7	0.73	0.13	42	0	7	291	37	39	83	2.8	0.04	0.23	52	0.38	1	3		
02.01	CQual	59.7	1.31	0.29	36.3	157	1.7	30	1.8	0.07	0.075	0.048	0	8	8	0	0.19	1.9	20.6	0.08	0.048	0.85	0.11	0.088	27	0	14	271	16	21	27	0.27	0.1	0.34	ND	0.38	ND	ND		
02.01	CQual	70.6	1.5	0.2	22.8	107	0.4	20.8	4.1	0.04	0.016	0.083	0	0	35	0	2.38	1	4.5	0.09	0.025	0.6	0.3	0.28	22	0	11	591	43	33	84	0.55	0.17	0.23	ND	0.38	ND	ND		
02.01	CQual	69.6	1.53	0.17	23.8	111	0.5	0	4.1	0.03	0.006	0.076	0	0	83	0	0.35	2.3	17.1	0.11	0.032	0.55	0.31	0.29	23	0	9	816	17	21	55	0.54	0.18	0.24	ND	0.4	ND	ND		
Nuts, seeds and their products																																								
03.00	T/CQual	5.25	21.2	50.6	6	4	7.85	4.4	0.6	11.8	4.19	31.8	13.5	0	0.5	3	0	25.8	0	<0.5	0.24	0.81	3.93	0.35	0.13	99.1	0	1.61	668	248	232	416	3	0.9	2.85	<61	1.39	<2.2	5.7	
03.00	T	2.6	22.0	52.8	3	8.29	2.77	4.72	11.8	4.05	33.66	12.65	0	0.1	1	1	0	26	0	0	0.07	0.86	3.85	0.23	0.13	33	0	1	746	266	286	489	4.51	1.17	3.54	ND	2.62	2.8	ND	
03.00	CQual	2.41	21.1	53.9	8.72	638	4.86	0.73	9.5	4.09	33.1	13	0	0	1	0	23.9	0	0	0.07	1.2	3.64	0.32	0.14	55	0	498	713	268	279	471	3.73	1.1	3.31	ND	2.23	ND	ND		
03.00	CQual	4.51	21.4	52.5	8.76	631	4.63	1	9.9	3.95	33.4	12.4	0	0	4	0	23.8	0	0	0.19	0.71	3.5	0.31	0.12	49	0	19	659	236	268	481	3.28	1.03	2.97	ND	1.84	ND	ND		
03.00	CQual	2.2	22.8	49.1	14.8	623	5.9	5	8.6	8.4	25.5	12.9	0	0	<5	10.3	2.46	<0.8	<0.5	0.43	0.024	10.6	1.76	0.4	89.3	0	8.6	700	57	190	400	1.6	0.46	3	23.6	1.4	30	<20		
03.00	T/CQual	1.55	23.6	49.6	8	6	15	631	4.22	8.87	8.04	24.9	13.6	0	0	0	2.5	0	<0.5	0.44	0.1	13.53	1.4	0.26	66.6	0	531	531	47.4	169	244	1.2	0.68	2.92	304	1.19	4.8	5.7		
03.00	T/CQual	1.55	23.6	49.6	8	6	13.9	632	3.13	10.8	8	6.89	24.64	15.69	0	0	6.93	0	0	0.44	0.1	13.53	1.4	0.26	145	0	6	658	54	176	358	2.26	0.67	3.31	ND	2.08	7.5	ND		
03.00	CQual	41.8	15.5	22	9.54	316	2.47	0	8.8	3.06	10.9	6.96	0	0	0	0	4.1	0	0	0.26	0.063	5.26	0.83	0.15	75	0	751	180	55	102	198	1.01	0.5	1.83	ND	1.02	ND	ND		
03.00	CQual	51	1.81	2.23	36.5	189	7.86	28.6	7.45	0.37	0.75	0.83	0	0	0	0	0.5	ND	41.6	0.22	0.1	1.47	0.48	0.35	60	0	3.25	550	27	34.5	69.8	0.94	0.33	0.51	ND	2.16	0.9	0.1		
03.01	CQual	5.52	5.69	3.43	70.4	362	0	46.9	12.6	0.52	0.97	ND	ND	ND	ND	ND	ND	ND	16	ND	2.1	1.53	0.58	215	ND	ND	ND	ND	61.6	67.9	ND	<0.1	0.5	1.1	ND	3.2	ND	ND		
03.01	CQual	64.1	2.01	1.38	27	139	0	22.8	4.5	0.26	0.48	0.55	0	0	10	0	1	ND	26.7	0.15	0.1	0.73	0.32	0.23	38	0	27	715	46	54	99	1.73	0.47	0.25	ND	0.85	2.2	0.1		
03.01	CQual	40.5	3.17	2.2	47.8	236	10.3	32	5.1	0.41	0.76	0.87	0	0	14	0	0.5	7.8	26	0.24	0.18	1.34	0.55	0.5	70	0	2	592	29	33	107	0.91	0.51	0.57	ND	1.18	ND	0.12		
03.01	CQual	62.7	1.96	1.4	28.8	145	3.9	17.4	4	0.4	ND	ND	0.2	ND	ND	ND	<0.1	ND	ND	<	0.05	0.07	1.5	0.44	0.22	58	ND	52.1	359	21.1	24.1	51	<1	ND	ND	4.5	ND	ND	ND	
03.01	CQual/MW6	33.3	1.28	0.67	63	266	0	11.5	1.3	ND	ND	ND	ND	ND	ND	ND	ND	ND	10.3	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	
03.01	CQual	34.6	0.96	0.7	60.2	258	43.2	16.9	3.2	0	ND	ND	ND	ND	ND	ND	ND	ND	2.27	ND	ND	ND	ND	ND	ND	ND	<10	174	11.3	12.2	ND	1.7	0.08	0.3	ND	0.24	1	0.4		
03.01	T/CQual/MW	5.31	14.9	60.7	5.36	607	6.28	4.34	0.48	9.7	4.46	45.65	7.92	0	2	11	0	15.0	14.2	6.3	0.64	0.11	1.8	0.92	0.56	121	0	0	680	114	163	290	4.7	1.73	2.45	18	6.18	2.4	16.8	
03.01	CQual	ND	13.4	61.2	7.67	664	2.91	4.76	9.43	6.43	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
03.01	CQual	2.52	14.4	66	5.21	702	4.26	0.96	9.4	4.51	46.6	8.46	0	0	36	0	15.3	ND	3.8	0.34	0.12	2.05	0.92	0.62	88	0	ND	755	123	173	310	4.38	1.75	2.5	3.08	5.55	ND	ND		
03.01	T/MW	4.07	15.2	65.2	3.3	688	2.6	0.7	6.7	6.13	8.93	47.17	0	2	12	0	0.7	2.7	1.3	0.34	0.15	1.13	0.57	0.54	66	0	2	441	98	158	346	2.91	1.59	3.09	24	3.41	4.9	9		
03.02	WA	5.3	17.7	44.4	27	585	0	0	3.1	ND	ND	ND	ND	ND	0	3	0	0.78	ND	0.3	0.6	0.18	1.5	ND	0.45	46	0	14	641	44	267	509	6.4	2.15	4.59	ND	ND	ND	ND	
03.02	T/CQual	1.7	15.3	46.3	26.7	632	8.01	17.7	3.85	10.5	26.7	9.05	0	0	0	0	0.75	34.7	<0.5	0.2	0.2	1.4	1.22	0.26	51.4	0	640	546	40.3	223	452	3.9	2	5.4	364	1.1	<5	6.2		
03.02	T	1.7	15.3	46.3	25.9	574	0	0	3	9.16	27.32	7.84	0	0	0	0	0.92	34.7	0	0.2	0.2	1.4	1.22	0.26	69	0	16	565	45	260	490	6	2.22	5.6	ND	0.83	11.7	11		
03.02	WA	6.3	22.4	45.9	14.6	578	0	0	8.5	ND	ND	ND	ND	ND	0	0	10.9	ND	0	0.87	0.14	15.5	ND	0.59	110	0	6	727	47	191	359	3.9	0.86	2.5	ND	ND	ND	ND		
03.02	T/CQual	3	6.88	12.9	3	690	6.64	0	16.3	57.2	2.75	0.71	0	0	0	0	0.44	0.3	1.5	0.06	0.1	0.6	0.8	0.3	16.5	0	37	543	26	90	206	3.32	0.8	2.01	ND	2.75	18.5	2.98		
03.02	CQual	47	3.33	33.5	6.22	360	6.22	0	9	29.7	1.43	0.37	0	0	0	0	0.24	0.2	3.3	0.06	0.02	0.54	0.3	0.054	26	0	20	356	14	32	113	2.43	0.44	1.1	ND	1.5	ND	ND		
03.02	CQual	45.8	3.6	33.5	7.15	365	6.23	0	9	29.7	1.43	0.37	0	0	0	0	0.24	0.2	3.3	0.06	0.02	0.54	0.3	0.054	26	ND	20	356	14	32	113	2.43	0.44	1.1	ND	1.5	ND	1.2		
03.02	T/CQual	2.03	21.3	45.9	17.2	617	7.57	3.23	3	5.56	24.22	13.9	0	26	157	0	1.93	13.2	3.2	0.84	0.16	1.43	0.51	1.27	94.2	0	405	1042	110	120	485	4.2	1.33	2.3	728	1.28	9.3	6.2		
03.02	T/CQual	1.99	21.3	45.9	17.9	608	10.0	7.26	10.3	5.56	24.22	13.9	0	26	157	0	1.93	13.2	2.3	0.84	0.16	1.43	0.51	1.27	50	0	10	1042	110	120	485	4.2	1.33	2.3	ND	1.28	9.3	ND		
03.02	T/MW/CQual	4.69	17.7	49.7	9.81	577	0.3	0.4	14.9	6.96	18.76	21.77	0	0.9	5	0	0.25	0	0	0.79	0.25	4.52	0.05	0.79	97	0	2.31	468	962	324	605	14.6	1.58	5.74	ND	1.24	26.5	<5		
03.03	CQual	5	17	48	9.14	582	0.48	0	16.9	6.72	18.1	21	0	0	40	0	0.25	0	0	1.21	0.47	5.44	0.68	0.15	96	0	39	406	131	346	774	7.78	1.46	10.2	ND	1.43	ND	ND		
03.03	CQual/MW6	3.38	21.3	55.5	10.1	653	2.62	3.8	6.4	6.23	10.9	35.6	0	0	30	0	42.3	0	1.4	1.98	0.16	4.8	0.83	1.24	254	0	5.5	578	86.5	364	477	4.9	1.5	3.8	ND	1.95	8.41	5		
03.03	CQual/MW6	1.2	19.3	48.8	15.1	618	2.73	0	9	5.22	9.51	32.9	0	0	5	0	26.1	2.7	1.4	0.11	0.25	7.04	0.8	0.8	217	0	655	850	70	129	1160	3.8	1.83	5.29	ND	2.11	ND	ND		
03.03	CQual/MW6	1.45	7.14	72.9	8.35	740	4.57	1.05	8.6	11.6	57.2	1.65	0	0	ND	0	0.54	ND	1.2	1.2	0.16	2.47	0.76	0.28	11	0	5	368	85	130	188	3.69	0.76	1.3	ND	4.13	ND	2		
03.03	CQual	1.61	7.04	70.2	9.95	724	4.4	4.2	9.5	11	54.7	1.38	0	0	0	0	0.57	0	0.7	0.71	0.087	2.27	0.6	0.36	10	0	360	363	70	118	198	2.65	0.57	1.29	ND	3.04	ND	ND		
03.03	CQual/MW6	5.93	20.2	36.6	6.6	506	1.55	0	27.3	3.17	6.51	24.9	0	0	0	0	0.31	4.3	0.6	1.22	0.2	3.08	0.99	0.63	93.7	0	20.5	641	228	372	595	10.2	1.22	6.05	ND	2.48	28	0.5		

09.03	Cqual/USDA	1.12	10.2	73	5	731	4.9	0.1	3	7.1	43.95	20.57	0	84	0	1.3	ND	0.7	0.45	0.107	1.167	0.703	0.187	16	0	400	424	72	132	293	2.8	1.167	5.07	ND	3.933	4	ND			
09.03	Cqual/USDA	5.8	16.5	30.7	7.72	454	0	0	34.4	3.33	2.31	23.7	0	ND	ND	0.5	ND	1.6	0.62	0.17	8.83	ND	ND	49	0	16	407	631	335	860	7.72	0.92	4.58	ND	2.72	55.2	ND			
Vegetables and their products																																								
04.00	T/WA/Cqual	87.71	2.97	0.79	6.33	47	0.95	0.36	3.3	0.13	0.3	0.12	0	842	5054	0	0.75	1640	133	0.09	0.1	1.31	0.4	0.09	170	0	56	554	138	50	58	6.2	0.15	1.07	364	0.16	0.1	< 5		
04.00	Cqual	3.95	29	5.34	16.8	291	7.27	0	29.7	1.38	0.76	3.12	0	1150	0	8.96	1360	137	0.62	2.32	10.2	1.79	1.14	187	0	422	4490	658	386	492	38	0.62	5.78	ND	5.57	ND	ND			
04.00	Cqual	11.3	13.5	7.02	58.6	369	1.68	56.9	6.7	1.46	1.69	2.78	0	1	0	1.19	0	4.2	0.12	0.2	0.92	1.46	0.59	82	0	4	508	159	248	557	7.61	0.53	2.87	ND	3.33	ND	ND			
04.00	T/MW	90.17	2	0.1	3	31	2.5	0.5	3.2	0.03	0.02	0.03	0	38	225	0	0.36	53	21.1	0.2	0.06	1	0.25	88	0	8	303	81	57	63	0.8	0.09	0.6	41	0.99	0.7	ND			
04.00	T/MW	95.27	0.68	0.1	1.9	16	1.9	0	ND	0.03	0.02	0.05	0	0.7	4	0	1.3	14.8	0.01	0.04	0.25	0.17	0.07	25	0	39	233	25	10	20	0.34	0.05	0.28	37	0.07	0.6	1			
04.00	T/Cqual	93.89	0.86	0.17	2.8	20	2.18	0	1.7	0.06	0.01	0.06	0	36	208	0	0.37	7.4	80.4	0.06	0.03	0.48	0.1	0.22	22.5	0	3	175	10	10	0.34	0.07	0.13	ND	0.12	0	1			
04.00	Cqual	8.05	12	17.3	29.4	376	10.3	0	27.2	3.26	2.75	8.37	0	0	ND	0	29.8	80.3	76.4	0.33	0.92	8.7	ND	2.45	106	0	30	2010	148	152	293	7.8	0.37	2.48	ND	2	ND	ND		
04.00	Cqual	92.1	0.8	0.27	4.55	26.8	2.7	0	1.5	0.07	0.1	0.02	0.16	0	< 2	834	< 0.5	1.44	ND	121	0.04	1	0.041	0.74	0.12	0.38	40.7	ND	8.4	155	7.7	11.9	22.5	0.4	< 0.1	0.13	61	0.1	0.1	< 5
04.00	T/Cqual/MW	83	1.5	0.3	4.9	61	3.15	0.3	1.8	0.04	0	0.17	0	166	1000	0	0.92	47	12	0.06	0.03	0.4	0.14	0.23	56	0	20	180	59	28	35	2.1	0.12	0.12	59	0.48	1	1.1		
04.01	T/Cqual	96.26	0.81	0.11	2.09	15.1	1.1	0	1	0.01	0	0.06	0	32	192	0	0.03	24.1	3.9	0.04	0.02	0.12	0.12	0.05	43.5	0	9	152	20	8	22	0.35	0.03	0.16	ND	0.13	0.5	3.3		
04.01	T/MW	91.87	0.9	0.1	4.7	28	4.5	0.2	1.8	0.01	0.01	0.05	0	0	0	0.1	0.03	ND	21	0.04	0.03	0.4	0.2	0.09	15	0	67	191	30	11	27	0.3	0.09	0.27	290	0.13	0.7	ND		
04.01	T/Cqual	90.21	1.24	0.2	2.3	31	2.21	0.09	3.1	0.04	0.033	0.081	0	14	578	0	0.58	62.8	12	0.01	0.03	0.64	0.23	0.05	27	0	52	414	49	17	50	0.73	0.07	0.2	ND	0.19	0.7	0.5		
04.01	T/MW	86	2.43	0.3	1.8	20	1.7	0.1	3.33	Tr	Tr	Tr	0	522	3132	0	ND	93	0.23	0.11	0.2	0.25	0.1	0.1	100	0	86	494	109	49	51	2.7	0.06	0.25	27	ND	ND	ND		
04.01	T/MW	91.4	2.86	0.39	1.6	23	1.5	0.1	1.6	0.06	0.01	0.17	0	938	5626	0	2.03	482.9	28.1	0.08	0.19	0.72	0.07	0.2	194	0	79	558	99	79	49	2.71	0.13	0.53	98	0.9	1	2		
04.01	T/WA	58.58	6.36	0.5	16.3	149	1.6	14.7	2.1	0.09	0.01	0.25	0	0	0	0	0.01	1.4	31.2	0.2	0.11	0.7	0.6	1.24	4	0	17	401	181	25	153	1.7	0.3	1.16	ND	1.67	14.2	ND		
04.01	Cqual/USDA	6.48	16.7	0.77	62.8	344	2.43	0	9.45	0.2	0.067	0.29	0	0	0	0	0.67	0.4	2.39	0.45	0.15	0.74	0.74	1.65	47	0	43	1150	79.5	67.5	416	4.2	0.53	2.81	ND	0.98	23.9	ND		
04.01	T	21.33	31	1.67	21.9	2.27	0	0	8.07	0.25	0.11	0.8	0	3706.6	2224	0	ND	ND	246.6	0.89	3.64	8.4	0.48	4	820	0	53.33	3726.6	426.6	553.3	3	31.73	1.7	5.27	ND	0.82	6	ND		
04.01	M1/T/Cqual	94.5	0.88	0.2	3.05	18	2.72	0	1.26	0.04	0.04	0.12	0	84	449	0	0.54	7.9	12.7	0.04	0.02	0.59	0.09	0.08	22.5	0	3.33	272.04	12.26	14.46	46.09	0.65	0.07	0.49	51	0.11	0	0.2		
04.01	T/Cqual	92.66	1.8	0.2	0.5	19	0.5	0	1.6	0.03	0.04	0.07	0	612	3647	<	1.89	830	30	0.04	0.09	0.4	0.17	0.1	14	0	2.13	379	51	81	46	1.8	0.18	0.36	221	0.37	0.9	< 20		
04.02	M1/T/Cqual	92.41	1.01	0.19	2.39	24	2.39	0	2.7	0.03	0.02	0.08	0	2	16	0	0.3	3.5	2.2	0.04	0.04	0.65	0.28	0.08	24.5	0	2	230	13.38	14	28.91	1.19	0.57	0.16	ND	0.25	0.3	ND		
04.02	T/Cqual	94.64	1.21	0.18	1.8	16	1.79	0	1.1	0.04	0.01	0.08	0	20	120	0	0.12	4.3	17	0.05	0.14	0.49	0.16	0.22	29	0	10	262	15	17	38	0.35	0.05	0.29	ND	0.18	0.2	1.64		
04.02	M1/T/WA/MW	96.73	0.59	0.16	2.16	15	1.46	0	0.7	0.01	0	0	0	8	31	0	0.03	7.2	3.2	0.03	0.03	0.04	0.24	0.05	6	0	2	136	13.26	12	45.9	0.62	0.03	0.23	17	0.07	0.1	3		
04.02	T/Cqual/MW	95.43	0.69	0.17	2.97	32.4	0.87	0.08	1.6	0.04	0.03	0.08	0	44	270	Tr	0.27	29.3	3.1	0.02	0.06	0.32	0.25	0.07	86.4	0	80	260	40	11	24	0.2	0.04	0.13	130	0.1	0.4	< 10		
04.02	T/Cqual	94.4	0.9	0.1	1.5	11	1.27	0	2	0.04	0.03	0.074	0	0	60	0	0.2	29.3	8	0.05	0.04	0.4	0.4	0.07	32	0	110	305	52	14	32	0.5	0.073	0.12	ND	0.1	0.046	ND		
04.02	M1/T/WA/Cqual	88.29	0.93	0.24	6.45	41	5.42	0.8	3	0.03	0.01	0.1	0	1204	5774	0	0.66	13.2	5.9	0.07	0.06	0.98	0.27	0.14	31	0	51.02	316.02	34.02	16.98	43.13	0.55	0.53	0.71	61	0.14	0.1	< 5		
04.02	Cqual/MW	80.6	1.54	0.4	12.5	64	4.8	6.2	4.7	0.2	0.5	0.2	0	0	0	1	22.5	11.5	0.09	0.01	1.95	0.6	0.1	67	0	8	505	45.5	23	74	0.6	0.05	0.72	49	0.48	0.2	0.25			
04.02	M1/T/WA/Cqual	88.54	0.92	0.08	6.25	42	4.8	1.16	1.4	0.02	0.02	0.05	0	0.2	1	0	0.02	0.4	6.4	0.05	0.03	0.08	0.12	0.15	16	0	3	144	30.59	10	58.43	0.82	0.028	0.96	61	0.13	0.5	2		
04.02	M1/T/Cqual	91.91	1.98	0.1	2.05	25	1.56	0.3	2.5	0.02	0.01	0.07	0	2	8	0	0.08	1.6	46.4	0.06	0.06	0.53	0.65	0.22	111	0	30	303	27.5	15	67.5	1.41	0.04	0.17	ND	0.16	0.6	0.8		
04.02	T/Cqual	84.94	3.27	0.15	5.02	47	0.99	0.6	5.4	0.04	0.01	0.06	0	0	0	0	0.19	14	11.7	0.07	0.07	1.05	0.34	0.12	68	0	94	370	44	60	90	1.28	0.23	0.49	ND	0.26	0.2	0.5		
04.03	T/Cqual	93.46	0.76	0.11	1.7	22	1.5	0.2	1.7	0.01	0.02	0.04	0	12	ND	0	0.19	ND	1.7	0.02	0.03	0.29	0.1	0.04	68	0	176	392	72	43	23	0.73	0.03	0.18	ND	0.13	1	0.095		
04.03	M1/T/Cqual/MW	87.58	1.61	0.17	9.1	50.6	6.76	0.6	1.37	0.03	0.03	0.06	0	4	20	0	0.04	0.2	4.9	0.03	0.04	0.33	0.16	0.07	100	0	78	325	27.2	23	49.4	0.75	0.42	0.31	59	0.33	0.7	0.5		
04.03	T/Cqual/MW	92.46	2.34	0.34	1.88	22	1.43	0	1.2	0.05	0.01	0.14	0	0	0	1.9	0.01	0.1	2.4	0.09	0.42	3.85	1.51	0.12	29	0.04	4	314	3	9	85	0.52	0.32	0.52	69	0.05	8.9	3		
04.03	T/Cqual	94.52	0.9	0.1	4	20.8	2.2	0	3.1	0.02																														









09.03 8	Ciqual/MW	62	16.9	19.7	1.33	257	0.52	0	0	12.6	4.84	0.65	79	174	57	0.4	0.19	2.3	0	0.03	0.28	0.1	0.14	0.037	7	2.28	237	76	545	20	354	0.44	0.011	2.92	990	0.03	16.3	37.2
09.03 9	Ciqual/MW	31.3	24.9	32.7	0	429	0.17	0	0	19.9	8.32	1.36	78.8	216	66	0.38	0.46	1.7	0	0.03	0.37	0.23	0.44	0.086	7.75	1.4	639	100	1160	44	762	0.84	0.091	3.03	1820	0.04	12.5	131
09.04 0	Ciqual/MW	52.5	17.3	25.5	0	343	0	0	0	16.3	7.78	0.82	95.8	204	192	0.39	0.47	ND	0	0.03	0.33	0.5	0.69	0.14	55	0.6	599	145	424	20	282	0.36	0.045	2.38	1020	<0.1	6.41	13.8
09.04 1	USDA	42.41	21.4	28.7	2.34	353	0.5	0	0	18.6	7.77	0.8	75	192	74	0.5	0.25	2.4	0	0.02	0.382	1.01	1.72	0.166	36	1.22	1146	256	528	23	387	0.31	0.04	2.66	ND	0.009	14.5	ND
09.04 2	USDA	52.26	6.15	34.4	5.52	350	3.76	0	0	20.2	8.9	1.48	101	303	59	0	0.86	2.1	0	0.02	0.23	0.091	0.517	0.056	9	0.22	314	132	97	9	107	0.11	0.018	0.5	ND	0.011	8.6	ND
09.04 3	M1/FAO/Ciqual	29.0	19.3	24	0	447	0	0	0	16.3	5.22	0.83	95.9	478	91	0.7	0.311	ND	0	0.14	1.19	2.4	0.52	0.08	4	0.1	346	48	895	54	729	1.9	0.63	1.59	1040	Tr	10.1	30
09.04 4	Ciqual/MW	69	4.45	3.6	22.2	139	18	1.65	Tr	1.93	1.09	0.16	12	37	8	0.07	0.16	ND	0	0.03	0.2	0.1	0.5	0.03	8	0.3	57.1	150	84.9	12.8	77	0.32	0.0084	0.31	100	0.004	<10	14.4
09.04 5	T	ND	4.6	6.9	7	181	0	0	0	0.29	4.6	ND	ND	21.55	71.84	ND	ND	ND	ND	0.69	ND	ND	ND	ND	ND	ND	66.09	ND	143.68	ND	ND	0.1	ND	ND	ND	ND	ND	ND

Eggs and their products

10.00 1	T	52.31	15.8	26.5	3.59	322	3.36	0	0	9.55	11.74	4.2	1234	391	88	2.69	2.58	0.7	0	0.18	0.53	0.02	2.99	0.35	146	48	109	129	5	390	2.73	0.08	2.3	ND	0.06	56	154		
10.00 2	T/Ciqual	75.84	12.5	9.83	0.27	147	0.27	0	0	3.1	3.81	1.36	423	141	10	0.86	0.97	0.3	0	0.07	0.48	0.07	1.44	0.14	47	1.29	140	134	53	12	191	1.83	0.1	1.11	ND	0.04	31.7	53	
10.00 3	MW6	75.1	12.5	10.8	0	147	0	0	0	3.1	4.7	1.2	385.0	190	Tr	1.8	1.11	0	0	0.07	0.35	0.1	1.3	0.12	39	1.1	140	130	57	12	200	1.9	0.08	1.3	160	Tr	11	53	
10.00 4	MW6	68.9	10.9	16.8	0.0	195	0.0	0.0	0	7.24	5.64	1.71	356.5	247	53	1.6	1.12	Tr	0.07	0.33	0.1	1.31	0.09	30	2.2	1024	117	51	12	175	1.65	0.07	1.1	1521	Tr	10	50		
10.00 5	M2	83.1	4.7	8.4	2.7	106	2.6	0.1	1.2	1.6	4.6	1.4	99.9	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND

Sugars, sweeteners and syrup

11.00 1	T	30.47	0.37	0.07	68.8	278	0	0	1.1	0.01	0.04	0	0	2	0	ND	0.12	0	8.8	0.02	0.08	0.04	0.02	0.02	11	0	32	77	20	4	19	0.49	0.1	0.06	ND	0.04	2	ND		
11.00 2	T/WA/Ciqual/MW	0.03	0	0	99.7	399	99.7	0	0	0	0	0	0	0	0	0	0	0	0	0	0.02	0	0	0	0	0	0	2	1	0	0	0.01	0	0	0	Tr	0	0.6	0.3	
11.00 3	T/WA/Ciqual/MW	17.1	0.3	0	81.3	327	78.9	1	0.89	0.2	0	0	0	0	0	0	0	0	0.5	0	0.04	0.12	0.07	0.02	2	0	4	52	6	2	4	0.42	0.04	0.22	18	0.08	0.8	Tr		
11.00 4	T	0.9	3.3	3.1	76.9	349	0	0	4.4	1.83	1.01	0.09	0	0.4	0	ND	0.05	1.1	0.7	0.03	0.15	0.51	0.05	0.01	7	0	210	591	37	98	128	3.14	0.71	1.55	ND	0.71	2.6	160		
11.00 5	T/USDA	1.07	5.41	29.7	62.1	54.0	5	0	5.4	5.39	16.28	6.77	0	2	1	0	4.96	1.9	0	0.12	0.17	0.43	0.36	0.08	14	0.28	41	407	108	64	152	4.38	0.47	1.06	ND	0.87	3.6	ND		
11.00 6	T/MW	1.5	7.65	29.6	56.9	535	56.9	0	3.4	14.2	13.23	0.81	23	50	0	0	2.02	ND	0	0.11	0.3	0.39	0.47	0.04	11	0.62	79	372	189	63	208	2.35	0.49	2.01	190	0.47	4.5	30		
11.00 7	Ciqual	7.83	3.88	23.8	60.2	475	53	3.9	3	18.4	3.81	0.51	5.5	8	11	0.5	0.18	ND	<0.5	0.04	0.18	0.47	0.27	0.21	25	0.17	200	331	78.8	46.8	103	1.8	0.3	0.8	155	0.6	1	11		
11.00 8	Ciqual	1.1	6.16	34.2	57.1	563	56	0	1	21.3	10.2	1.06	23	6.5	75	Tr	1.14	ND	0	0.08	0.49	0.2	0.59	0.07	10	Tr	88	350	281	26.5	230	0.2	Tr	0.9	ND	Tr	3	0.8		
11.00 9	Ciqual	1.7	9.5	25	55.9	499	50.5	3.4	5.9	9.87	12.7	1.24	ND	ND	10.6	0.75	2.32	2.07	ND	0.34	0.17	2.29	0.78	0.034	80.4	ND	47	500	100	95	230	2.9	0.52	1.4	131	0.7	<20	<20		
11.01 0	M2	13.6	12	25.6	42	447	13.2	28.7	6.5	3.9	15.8	4.4	15.3	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
11.01 1	T	76.1	0.5	0	23.1	92	0	0	0.1	0	0	0	0	27	ND	0	0.05	ND	25.7	0.01	0.03	0.16	0.02	0.02	22	0	8	100	9	8	13	0.47	0.02	0.02	ND	0	0.55	0		
11.01 2	USDA	21.1	6.2	0	71.3	318	71.3	0	0	0	0	0	0	0	0	ND	ND	ND	0	0.01	0.39	8.12	0.171	0.5	12	0	35	320	61	72	236	0.96	0.2	0.14	ND	0.1	12.3	ND		
11.01 3	USDA	22.7	0	0	74.9	290	74.9	0	0	0	0	0	0	0	0	0	0	0	0	0.1	0.155	0.1	0.804	0.67	0	0	8	1000	150	100	56	3.8	0.13	0.41	ND	1.53	1.7	ND		
11.01 4	M1/T	32.4	0	0	66.6	266	0	0	0	0	0	0	0	0	0	ND	0	0	0	0	0.01	0	ND	0	0	0	27	28	6	4	4	0.05	0.03	0.13	ND	ND	0.6	ND		
11.01 5	Ciqual	32.3	0.04	0.06	67.1	269	62.6	0	0	0.00	0.011	0.017	0	0	0	0	0	0	0	0.06	1.27	0.081	0.036	0.002	0	0	6.57	219	106	21	2	0.11	0.018	1.09	ND	2.6	ND	ND		
11.01 6	Ciqual	21.8	0.5	0.5	78.1	318	70.2	0	0	0.25	0.01	<	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
11.01 7	USDA	37.98	0	0	61.4	234	21.4	7	0	0	0	0	0	0	0	0	0	0	0	0.02	0.008	0	0.004	0	0	0	82	15	3	2	9	0.03	0	0.08	ND	0.068	0	ND		
11.01 8	USDA	87	0.8	0	12.1	52	0.01	0	0.7	0	0	0	0	0	0	0	0	0	0	0	0	0	0.002	0	0	0	0	210	0	0	0	0	0	0	0	0	0	0.5	ND	

Beverages (alcoholic and nonalcoholic)

12.00 1	M1/T/Ciqual	88.3	0.7	0.2	9.44	45	8.4	0	0.2	0.02	0.04	0.04	0	20	33	0	0.04	0.1	50	0.09	0.03	0.4	0.19	0.04	30	0	1	200	11	17	0.2	0.04	0.05	ND	0.01	0.1	2	0.4
12.00 2	Ciqual	89.7	0.63	0.13	7.83	38.5	7.83	0	0.25	0.03	0.035	0	0	10.6	0	0.15	0	44.2	0.08	0.034	0.3	0.24	0.1	30	0	3.44	154	7.25	10.9	16.9	0.08	0.023	0.022	ND	0.02	<10	0.4	
12.00 3	Ciqual	88.2	0.61	0.11	9.98	45	9.98	0	0.28	0.05	0.015	0.018	0	0	26.2	0	0.2	0.1	37	0.08	0.023	0.3	0.24	0.1	30	0	4.81	165	0.41	10	16.5	0.068	0.022	0.045	ND	0.023	ND	0.7
12.00 4	M1/Ciqual	90	0.44	0.1	7.8	38.1	7.8	0	0.1	0.01	0.013	0.024	0	0	4	0	0.22	0	38	0.04	0.02	0.2	0.19	0.044	10	0	1	162	9	12	15	0.2	0.033	0.05	ND	0.02	ND	0.6
12.00 5	Ciqual	89.9	0.49	0.08	7.83	38.2	7.83	0	0.15	0.04	0.005	0.017	0	0	21.7	0	0.19	ND	22.5	0.04	0.017	0.12	0.13	0.048	12.6	0	3.05	128	4.83	8.63	15	0.15	<0.1	<0.1	<60	<0.1	ND	1
12.00 6	M1/Ciqual	88	0.66	0.14	10.6	ND	10	0	0.15	0.04	0.03	0.035	0	0	30	0	0.09	ND	17.6	0.07	0.018	0.25	0.13	0.066	19	0	3.79	123	2.8	9.3	0.3	<0.1	<0.1	<60	<0.1	0.5	1	















## Abréviations

Prot	Protein	Betac	Betacarotene	Na	Sodium
Fat	Fats	Vit D	Vitamin D	K	Potassium
CHO	Carbohydrates	Vit E	Vitamin E	Ca	Calcium
E	Energy	Vit K	Vitamin K	Mg	Magnesium
Sug	Sugars	Vit C	Vitamin C	P	Phosphorus
Sta	Starch	Vit B1	Vitamin B1	Fe	Iron
Fiber	Fib	Vit B2	Vitamin B2	Cu	Copper
SFA	Saturated fatty acids	Vit B3	Vitamin B3	Zn	Zinc
MUFA	Monounsaturated fatty acids	Vit B5	Vitamin B5	Chlor	Chloride
PUFA	Polyunsaturated fatty acids	Vit B6	Vitamin B6	Mn	Manganese
Chol	Cholesterol	Vit B9	Vitamin B9	Se	Selenium
Vit A	Vitamin A	Vit B12	Vitamin B12	I	Iodine

## Sources

M1	Moroccan FCT (1984)
M2	CIRIHA source
T	The FCT of Tunisia
WA	The West African food composition table
Ciqual	The French food composition table
MW	The McCance and Widdowson's tables (UK)
USDA	The USDA Food Composition Database

## Codes des aliments

Food code	Name	Starchy roots, tubers and their products	Fruits and their products
01.001	Rye, raw	02.001	06.001
01.002	Oats, raw	02.002	06.002
01.003	Quinoa, raw	02.003	06.003
01.004	Wheat, durum, dry	02.004	06.004
01.005	Wheat, soft	02.005	06.005
01.006	Wheat, whole grains, raw	02.006	06.006
01.007	Soya, dry	02.007	06.007
01.008	Corn, dry	02.008	06.008
01.009	Rice, white, raw	02.009	06.009
01.010	Rice, brown, raw	02.010	06.010
01.011	Rice, red, raw	02.011	06.011

01.012	Sorghum, whole grain, raw	02.012	Taro, tuber, raw (Taro, racine, crue)	06.012	Mangoes, raw
01.013	Sorghum, whole grain, white, raw	02.013	Yam, raw (ligname, crue)	06.013	Apricots, raw
01.014	Barley, dry			06.014	Nectarines, raw
01.015	Bareley, soup (Tchicha bel marka)	<b>Nuts, seeds and their products</b>		06.015	Plum, raw
01.016	Barley, semolina, with milk (Tchicha bel halibe)	03.001	Almond (with skin)	06.016	Prune, dried
01.017	Semolina, barley (Smida)	03.002	Almond nuts, dry , roasted , unsalted	06.017	Kiwi, raw
01.018	Semolina, wheat (Tchicha)	03.003	Almond, roasted, salted	06.018	Lemon, raw
01.019	Semolina, corn (Smida d dra)	03.004	Almond, hulled, pruned or bleached	06.019	Orange, raw
01.020	Couscous, dry	03.005	Peanut	06.020	Mandarine, raw
01.021	Couscous, semolina	03.006	Peanut, roasted, salted	06.021	Grapefruit, raw
01.022	Couscous, with legums	03.007	Peanut, roasted, unsalted	06.022	Figs, raw
01.023	Couscous, with meat and legumes	03.008	Peanut, boiled, salted	06.023	Figs, dried
01.024	Couscous, with poultry and dried grapes	03.009	Chestnut, raw	06.024	Olive, ripe, in brine
01.025	Couscous, with onion	03.010	Chestnut flour	06.025	Olive, green, in brine
01.026	Couscous, with leben (saikok bel leben)	03.011	Chestnut, boiled	06.026	Dates, dried
01.027	Couscous, with milk	03.012	Chestnut, roasted	06.027	Dates, with almonds (temere b louze)
01.028	Seffa (chariya mefeouara)	03.013	Chestnut, canned		
01.029	Vermicelli boiled, with milk	03.014	Chestnut, cream	<b>Condiments and sauces</b>	
01.030	Mehamessa, with milk	03.015	Chestnut, cream, with vanilla, canned	07.001	Tomato paste, unsalted
01.031	Pizza dough, raw	03.016	Hazelnut	07.002	Cinnamon, dried
01.032	Edess, with tomato	03.017	Hazelnut, roasted, salted	07.003	Gherkin pickle
01.033	Pasta, white, Spaghetti	03.018	Hazelnut, roasted, unsalted	07.004	Cumin, powder
01.034	Pasta, white, raw (Macaroni)	03.019	Walnut, dry	07.005	Turmeric, powder
01.035	Spaghetti , wholemeal, raw	03.020	Cashew nut	07.006	Curry, powder
01.036	Brewer's yeast, dry	03.021	Cashew nuts, roasted, salted	07.007	Ginger, ground
01.037	Oats, bran	03.022	Cashew nut , roasted , unsalted	07.008	Salad cream (Mayonnaise)
01.038	Wheat, bran	03.023	Groundnut , raw	07.009	Mint, fresh
01.039	Corn, bran	03.024	Coconut, dry	07.010	Mustard, prepared (Moutarde)
01.040	Rice, bran	03.025	Coconut, immature kernel, fresh, raw	07.011	Red pepper, dried, ground
01.041	Rye, flour	03.026	Coconut, mature kernel, fresh, raw	07.012	Black pepper, ground
01.042	Wheat, flour, white	03.027	Pistachio nuts, roasted, salted	07.013	Cider vinegar
01.043	Barley, flour	03.028	Pistachio nut, roasted, unsalted	07.014	Ground thyme
01.044	Soya , flour	03.029	Sesame seeds, dried	07.015	Saffron
01.045	Rice, flour	03.030	Sesame, seeds, roasted	07.016	Paprika
01.046	Corn, flour	03.031	Sunflower seed	07.017	Clove
01.047	Chick pea, flour	03.032	Sunflower, seed, roasted, salted	07.018	Béchamel sauce
01.048	Cornstarch	03.033	Macadamia nuts	07.019	Mustard Sauce
01.049	Corn flakes	03.034	Macadamia nuts, roasted, salted	07.020	Harissa (condiment sauce)
01.050	Bread, whole meal, durum wheat	03.035	Flaxseed	07.021	Tomato sauce, with onions
01.051	Bread, white, French stick	03.036	Pecans, salted	07.022	Laurel
01.052	Mellaoui (Mellaoui)	03.037	Chia seed, dried	07.023	Tomato ketchup
01.053	Bread, rye			07.024	Salt
01.054	Bread , toasted	<b>Vegetables and their products</b>		07.025	Aromatic herbs (Mint basilic, parsley basil coriander)
01.055	Bread of panini	04.001	Parsley, raw		
01.056	Bread of hamburger	04.002	Parsley, dried	<b>Fat and oils</b>	



01.102	Cake, with yogurt		
01.103	Cake, with sesame seeds (Haloua d zeljelane)		
01.104	Cake, with datte (Gato be temere)		
01.105	Pancake, roll		
01.106	Basbousa Maqrout		
01.107	Cake, coconut		
01.108	Sellou (Zammita)		
01.109	Chabbakia, Mkharrka		
<b>Milk and their products</b>			
09.001	Milk, whole, cow, condensed sweetened		
09.002	Milk, whole, goat		
09.003	Skim milknddry with water (Leben)		
09.004	Milk, skimmed		
09.005	Milk, semindskimmed		
09.006	Whole milkndproducer, 3.7 % Fat (Raib)		
09.007	Yourt, whole milk, flavored		
09.008	Yogurt, semindskimmed, flavored		
09.009	Yogurt, semindskimmed, plain		
09.010	Yogurt, whole milk, with fruits		
09.011	Yogurt, whole milk, chocolate		
09.012	Greek yogurt, sheep's milk		
09.013	Greek yogurt, with fruits		
09.014	Yoghurt, goat's milk, nature, 5% MG approx.		
09.015	Yogurt, fermented milk or dairy specialty, cereals, 0% MG		
09.016	Yoghurt, fermented milk or dairy specialty, flavored, with sweeteners, 0% MG		
09.017	Yoghurt, fermented milk or dairy specialty, flavored, sweet		
09.018	Yogurt, fermented milk or dairy specialty, flavored, sweetened, with cream		
09.019	Yogurt, fermented milk or dairy specialty, cereals		
09.020	Yoghurt, fermented milk or dairy specialty, chocolate chips, cream, sweet		
09.021	Yoghurt, fermented milk or dairy specialty, with fruit, with sweeteners, 0% MG		
09.022	Yogurt, fermented milk or dairy specialty, fruits, sweeteners, 0% MG, with vitamin D		
09.023	Yoghurt, fermented milk or dairy specialty, with fruits, sweet		
09.024	Yogurt, fermented milk or dairy specialty, with fruit, sweet, 0% MG		
09.025	Yoghurt, fermented milk or dairy specialty, with fruit, sweet, cream		
09.026	Yogurt, fermented milk or dairy specialty, fruits, sweetened, with vitamin D		
09.027	Yoghurt, fermented milk or dairy specialty, nature		
09.028	Yogurt, fermented milk or dairy specialty, nature, 0% MG		
09.029	Yogurt, fermented milk or dairy specialty, nature, with cream		
09.030	Yogurt, fermented milk or dairy specialty, nature, sweet		
09.031	Processed cheese spread		
09.032	Semi hard cheese		
09.033	Ricotta cheese		
09.034	Cheddar (Hard cheese)		
09.035	Edam (Red cheese)		
09.036	Gouda cheese		
05.007	Chickpeas, dried		
05.008	Chickpeas, houmous deouaze		
05.009	Peas, Canned		
05.010	Pease pudding (Bissara diale jelbana)		
05.011	Fenugreek, seed, ground		
05.012	Fenugreek seeds		
<b>Meat and poultry and their products</b>			
13.001	Beef flank, raw		
13.002	Beef, coast, raw		
13.003	Beef, shoulder, raw		
13.004	Beef, rib steak, lean, grilled (panndfried)		
13.005	Beef, ribeye, roasted		
13.006	Beef, steak, Grilled		
13.007	Beef, minced steak 5% MG, raw		
13.008	Beef, minced steak 5% MG, cooked		
13.009	Beef, minced steak 10% MG, raw		
13.010	Beef, minced steak 10% MG, cooked		
13.011	Beef, minced steak 15% MG, raw		
13.012	Beef, minced steak 15% MG, cooked		
13.013	Beef, minced steak 20% MG, raw		
13.014	Beef, minced steak 20% MG, cooked		
13.015	Veal, coast, raw		
13.016	Veal, rib, grilled (panndfried)		
13.017	Veal, square, sauteed (panndfried)		
13.018	Veal, square, raw		
13.019	Veal, escalope, cooked		
13.020	Veal, escalope, raw		
13.021	Veal, walnut, raw		
13.022	Veal, walnut, grilled (panndfried)		
13.023	Veal, walnuts and toast		
13.024	Veal, filet		
13.025	Veal, fillet, roast/ baked		
13.026	Veal, ground steak 20% MG, raw		
13.027	Veal, minced steak 15% MG, raw		
13.028	Veal, breast, raw		
13.029	Veal, roasted, raw		
13.030	Veal, roasted, cooked		
13.031	Veal, shoulder, raw		
13.032	Veal, shoulder, grilled (panndfried)		
13.033	Veal, shoulder, braised or boiled		
13.034	Veal, foot		
13.035	Veal, shank, braised or boiled		
13.036	Veal, head, boiled		



12.008	Tomato juice, pure juice, salted at 3g / L		
12.009	Grape juice	13.082	Ham, dried
12.010	Grape juice, concentrate based	13.083	Ham, dried, pama
12.011	Lemon juice	13.084	Ham, dried, Serrano
12.012	Lemon juice, home	13.085	Ham, dried, defatted
12.013	Lemon juice, pure juice	13.086	Ham, raw, smoked, lightened in fat
12.014	Pineapple juice	13.087	Bayonne ham
12.015	Pomegranate juice	13.088	Chicken ham
12.016	Apple juice, pure juice	13.089	Turkey ham
12.017	Apple juice, concentrate based	13.090	Jambonneau, cooked
12.018	Carrot juice, pure juice	13.091	Khlaa, sheep meat dried, salted, cooked in fat
12.019	Prune juice	13.092	Qaddid, beef meatdried, salted
12.020	Mango juice	13.093	Liver beef, roasted
12.021	Pineapple juice, pure juice	13.094	Liver lamb, raw
12.022	Smoothie	13.095	Liver calf, raw
12.023	Multifruit juice, pure juice	13.096	Liver calf, roasted
12.024	Multifruit juice, pure juice, multivitamin	13.097	Liver poultry, Raw
12.025	Multifruit juice, orange base, multivitamin	13.098	Brain lamb, raw
12.026	Multifruit juice, concentrate based	13.099	Paw, raw
12.027	Apricot nectar	13.100	Paw, with chickpea sauce
12.028	Papaya nectar	13.101	Brain, calf, raw
12.029	Pear nectar	13.102	Lamb kidney, raw
12.030	Passion fruit nectar	13.103	Beef kidney, raw
12.031	Banana nectar	13.104	Beef Tripe, raw
12.032	Mango nectar		
12.033	Fishing nectar	<b>Fish and their products</b>	
12.034	Orange nectar	14.001	Blue fish (Sardine, Bouri, Anchovy, Herring, Mackerl), raw
12.035	Multifruit nectar	14.002	White fish (Sole, Merlan, Bass, Hake, Mullet, Rockfish), raw
12.036	Apricot with light syrup, drained, canned	14.003	Shrimp, raw
12.037	Apricot with light syrup, not drained, canned	14.004	Squid, raw
12.038	Apricot with syrup, drained, canned	14.005	Squid, dried
12.039	Apricot with syrup, not drained, canned	14.006	Small clam, raw
12.040	Pineapple with syrup and pineapple juice drained, canned	14.007	Tuna, oil canned
12.041	Pineapple with syrup and pineapple juice, not drained, canned	14.008	Herring, raw
12.042	Pineapple with light syrup, drained, canned	14.009	Mussel, raw
12.043	Pineapple with light syrup, not drained, canned	14.010	Conger, raw
12.044	Peach with light syrup, drained, canned	14.011	Chinchar, raw
12.045	Peach with light syrup, not drained, canned	14.012	Swordfish, raw
12.046	Pear with light syrup, not drained, canned	14.013	Hake, raw
12.047	Mineral water, Sidi Ali	14.014	Gurnard, raw
12.048	Mineral water, Sidi Harazem	14.015	Mullets fish, raw
12.049	Mineral water, Ain Atlas	14.016	Mackere], raw
12.050	Mineral water, Ain Ifrane	14.017	Sea perch fish, raw
12.051	Mineral water, Soltane	14.018	Pageot, raw
12.052	Mineral water, Bahia	14.019	Ray, raw
		14.020	Rascass, raw

12.053	Mineral water, Oulmes	
12.054	Tea, brewed	
12.055	Tea, chinese, leaves, brewed	
12.056	Tea, flavored, sugar reduced	
12.057	Tea drink, flavored, sweetened	
12.058	Coffee prepared, instant	
12.059	Zizwa (coffee, liquid)	
12.060	Chocolate milk	
12.061	Cola, sweetened	
12.062	Cola, sweetened, without caffeine	
12.063	Coca Cola, soda	
12.064	Lemonade, sweetened	
12.065	Tonic or bitter, sweetened	
12.066	Soft drink, with fruits (10 to 50% juice), sweetened	
12.067	Soft drink, with fruits (10 to 50% juice), unsweetened	
12.068	Soft drink, without fruit juice, with reduced sugar content	
12.069	Soft drink, without fruit juice, sweetened	
12.070	Fruit drink, flavored (less than 10% juice), unsweetened	
12.071	Flat fruit drink (less than 10% juice), sweetened	
12.072	Fruit juice (with less than 10% juice), sweetened	
12.073	Fruit juice (less than 10% juice), sweet	
12.074	Diabolo (lemonade and syrup)	
12.075	Drink prepared, syrup of mint or strawberry, sweetened, diluted	
12.076	Energy drink, sweetened	
12.077	Beer (5G/100G alcohol)	
12.078	Wine, red	
12.079	Wine, white, foamy	
12.080	Wine, rose	
12.081	Spirits 40%	
14.021	Sar fish, raw	
14.022	Bonite, raw	
14.023	Sole, raw	
14.024	Sardine, raw	
14.025	Sardine, canned	
14.026	Oyster, raw	
14.027	Anchovy, raw	
14.028	Anchovy, canned	
14.029	Octopus, raw	
14.030	Octopus, dried	
14.031	Cuttlefish, raw	
<b>Prepared foods</b>		
15.001	Tajine, red meat, with potatoes	
15.002	Tajine, red meat, with sweet potatoes	
15.003	Tajine, red meat, with JerUSDAlem artichokes	
15.004	Tajine, red meat, with potatoes and peas	
15.005	Tajine, red meat, with carrots	
15.006	Tajine of red meat with beans	
15.007	Tajine, red meat, with carrots and peas	
15.008	Tajine, red meat, with carrots, peas and patatos	
15.009	Tajine, red meat, with Beans	
15.010	Tajine, red meat, with artichokes and peas	
15.011	Tajine, red meat, with zucchini	
15.012	Tajine, red meat, with zucchini and peas	
15.013	Tajine, red meat, with gourds (Slawiya)	
15.014	Tajine, red meat, with gombos	
15.015	Tajine, red meat, with cardoons	
15.016	Tajine, red meat with almonds	
15.017	Tajine, red meat with plums	
15.018	Tajine, red meat, with quinces	
15.019	Pastilla, with Chicken (bastilla d tja)	
15.020	Soup with tomato (Harira)	
15.021	Pizza, cheese and tomato	
15.022	Pizza, ham cheese	
15.023	Pizza, meat, bolognese	
15.024	Pizza, seafood	
15.025	Pizza, cheese mushrooms	
15.026	Pizza, tuna	
15.027	Pizza, chicken	

## **Annexe II : The EDSMAR Study**

### Design de l'étude

The EDSMAR Study (<http://edsmar.iarc.fr/>) - Etude de Déterminants de Cancer du Sein chez les Femmes Marocaines- est une étude cas-témoins multicentrique en population générale sur le cancer du sein au Maroc. C'est une étude collaborative menée en partenariat entre le CIRC, l'Institut de Recherche sur le Cancer de Fès (IRC) et l'Institut National d'Oncologie de Rabat (INO). Le recrutement est actuellement en cours, il est effectué au niveau de CHU Hassan II de Fès et à l'Institut National d'Oncologie de Rabat.

Au total, 500 cas et 500 témoins seront recrutés dans cette étude.

### Sélection des cas et témoins

Les cas sont (1) des cas incidents de cancer du sein primaire (in situ ou invasif) confirmés histologiquement et diagnostiqués ; (2) en mesure de participer et de fournir des échantillons biologiques (3) avant le début de tout traitement de la tumeur (chimiothérapie, radiothérapie, hormonothérapie ou chirurgie) ; et 4) en mesure de fournir un consentement éclairé signé pour la participation à l'étude.

Pour recruter les témoins, les cas seront invités à amener une amie ou une voisine (pas quelqu'un de la famille) du même âge (+/- 5 ans) et qui n'a jamais eu de cancer du sein ou d'autres cancers, et qui réside dans le même quartier que la patiente. Si cela est impossible, des alternatives de recrutement de témoins seront faites (Ex. recrutement des accompagnatrices des malades soignés dans les centres de l'étude...).

Les femmes enceintes, allaitants, ou suivies pour une insuffisance rénale chronique (cas ou témoins) sont exclues de cette étude.

### Recueil des données

En plus des données déjà détaillées lors de notre présentation de l'étude BreCaFez Study (partie 2 chapitre II), d'autres informations seront collectées dans le cadre de cette étude. Il s'agit de :

- ▷ Des informations détaillées sur perception de l'état de santé, le stress, et le bonheur dans la vie.
- ▷ Des mesures anthropométriques supplémentaires (ex. masse maigre, masse grasse, masse musculaire et squelettique, eau corporelle totale...) collectées à l'aide de la machine d'impédance.

### Collecte d'échantillons biologiques

Un protocole standardisé validé par le CIRC pour la collecte d'échantillons biologiques est utilisé dans cette étude. Le timing de l'ensemble des opérations sera enregistré (ex. le temps entre la préparation des échantillons et leur stockage). Les données suivantes seront collectées lors de la collecte de sang et d'urine : date et l'heure, l'état de jeûne, la date du premier jour du dernier cycle menstruel chez les femmes en préménopause, l'utilisation de



médicaments ou de compléments alimentaires dans la semaine précédente la récolte de l'échantillon biologique etc.

Un échantillon de sang de 20 ml sera obtenu par prélèvement veineux des sujets en position assise semi-verticale, pour récupérer sérum, plasma, globules rouges et couche leucocytaire. Des échantillons urinaires seront collectés dans des flacons en plastique spécialement conçus pour la collecte d'urine et conservés réfrigérés jusqu'à leur aliquotage dans 1ml-tubes et stockés à -80 ° C.

#### Récolte des échantillons de tumeurs

Les caractéristiques tumorales (le type histologique, le grade histopronostique de Scarff, Bloom et Richardson (SBR), la taille tumorale, l'implication des ganglions lymphatiques) et le statut des récepteurs hormonaux (œstrogène, progestérone, HER2) seront déterminés pour chaque cas inclus dans l'étude. Les sous-types moléculaires de cancer du sein seront déterminés (luminal A, luminal B, basal, ERBB2 et normal) en se basant sur les biomarqueurs d'immunohistochimie (ER, PR, HER2, EGFR, CK5 / 6, Ki67). Les analyses de l'ADN tumoral seront effectuées pour identifier les mutations TP53.

#### Création d'une biobanque

Dans cette étude, il est prévu de créer une biobanque qui comprend des échantillons de sang, d'urine, et des tissus tumoraux. pour à des fins de recherche scientifique basée sur les données des biomarqueurs (paramètres moléculaires, polymorphismes génétiques, biomarqueurs de l'alimentation et du métabolisme en particulier des acides gras, la vitamine D, l'acide folique et de vitamines antioxydants, les hormones et adipokines, les contaminants, la métabonomique).

#### Financement

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